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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

JUNE, 1926

ORIGINAL ARTICLES.

PSYCHONEUROSES.*

By Pierre Janet,

PROFESSOR OF EXPERIMENTAL AND COMPARATIVE PSYCHOLOGY, COLLÈGE DE FRANCE, PARIS, FRANCE.

Hysteria is a most important disease which was studied with special interest and intensity in the years between 1880 and 1895, during which period the scientific articles published on this topic became more numerous every year. This increase in interest was coincident with the rise of the School of Charcot at the Salpétrière Hospital. In the early eighties more than three thousand articles on this subject were published in medical journals each year. Subsequently there was a pronounced decline of interest and of literary expression, until now it is very rarely that one finds anywhere an expression of medical opinion upon hysteria. This is due to causes which I shall consider.

The study of the phenomena of hysteria is by no means merely modern. From the earliest times there have been religious miracles and healings by magic. Charcot in an article entitled "La foi qui guérit"[1] discussed the nature of the cures which took place in ancient times in the temple of Æsculapius at Epidaurus. From Epidaurus to Lourdes, history shows many instances of truly remarkable recoveries from apparently serious maladies—and at all times there have been scholars or scientists who endeavored to find an explanation other than the merely miraculous for these

* Being the substance of a lecture delivered at the Philadelphia General Hospital, October 14, 1925, translated and revised with the aid of Dr. Elton Mayo.

[1] Arch. de neurol., 1893.

cures. The would-be scientific doctrines of the magnetists were, for example, anticipated by Goclenius, Fludd (1574) and Vindingius (1673).

The nineteenth century interest in hysterical phenomena was derived chiefly from enquiries into the work of Mesmer and from the researches of the Marquis of Puységur in the later eighteenth century in France. Puységur used the term *somnambulism* to describe the sleep-walking condition of his subject Victor. In this sleep-walking condition Victor obeyed Puységur's commands and showed a greater degree of intelligence therein than had characterized him in his other state. Although this particular subject had, for no known reason, substituted this condition for what had formerly been some kind of attack or fit, Puységur (and also Deleuze) was inspired by the incident to study artificially induced somnambulism.

Following upon this type of investigation and discovery, an attempt was made to explain the bizarre phenomena of the neuroses and the many peculiar symptoms of epilepsy, hysteria, neurasthenia and the like on the basis of "animal magnetism." Those who undertook the investigation were not merely biologists and medical practitioners; inquirers were attracted from the ranks of mathematics, other sciences, and persons of general culture. The phenomena later described by Charcot and his school were first described by these observers; in many instances they even employed the very terms which Charcot later used. In these days, the study of these early investigations is much neglected, and not altogether wisely. Influences affecting the present development of psychopathological study are derived from these historic sources to an extent which is unsuspected by our own generation.

The exponents of animal magnetism soon split into two well-defined and opposing groups—the Fluidists and the Animists. The Fluidists represent an endeavor to move in the direction of a science of mechanism; they attempted to explain the bizarre phenomena of the neuroses as due to modifications of "the nervous fluid." The Animists showed no such tendency to mechanical explanation; they endeavored to describe hysteria and hypnosis in terms of thought and imagination. Mesmer, Deleuze and Dupotet must be ranked as representative Fluidists; Bertrand, Ordinaire and Noizet are equally representative of the other school. The mental attitude of each school was utterly dissimilar from that of the other; so also was its manner of reasoning. The Fluidists at first displayed the more scientific tendency in that they sought to assemble the various phenomena in the form of a precise explanation after the fashion of the physical sciences. Their misfortune was that they hunted for a precise physical cause in situations where no such cause could be demonstrated with the powers at their command. The virtue of the Animists was that, being burdened by no urgent necessity to

find a precise physical cause, they made more accurate observations than their rivals. Their closer observation led them to the conclusion that scientific precision and logic were not easily possible. They considered that the symptoms of hysteria were more of a piece with erratic psychological phenomena and the vagaries of the human mind. Charcot's studies at the Salpétrière began at a time when these two groups had been contending for many years. He was, nevertheless, ignorant of their work and developed a point of view peculiarly his own.

Charcot was a neurologist of high standing in the scientific world. He had been remarkably successful in diagnosing the symptoms of patients suffering from diseases of the spinal cord. He proposed to apply the same methods to the study of hysteria and hypnosis. He held that the study of psychological problems was usually begun wrongly—the most complicated problems being considered before the simple. As a prelude to the study of patients in abnormal mental states, he therefore set himself the task of ascertaining the precise symptoms of abnormal states—symptoms which could not be counterfeited. For him the abnormalities which could not be counterfeited were changes in muscular reflexes, variations of sensation and the like.

His paper, read before the Academy of Sciences in February, 1882, created something of a sensation. His attitude to hysteria and hypnotism was that they were symptoms of a disease which could be studied like any other disease. He specified three phases of hypnosis—lethargy, catalepsy, somnambulism—as organic symptoms which might be taken as definite signs of hysteria. His paper led to that sudden rise of interest in hysteria which I mentioned at the beginning of my address. His fellow scientists believed that Charcot had finally disposed of "animal magnetism" and had begun a scientific explanation of the curious and astonishing symptoms of the neuroses.

In spite of the immense following which Charcot thus gained, he failed in the end because he had not sufficiently safeguarded himself. Far from disposing of "animal magnetism," he had in a sense revived it in a new form. The magnetizers had been practising their art in France for almost a century when Charcot began his researches at the Salpétrière. Of the 5000 patients in the hospital, there were many who had been in the hands of the magnetisers; few who had not, somehow or other, come into contact with their ideas. Even Charcot's medical colleagues had been, however unwittingly, infected with their methods and beliefs. I myself had evidence of the far-reaching effects of the traditions of animal magnetism when I had occasion, in 1882, to examine a woman patient in a part of France very remote from Paris and the Salpétrière. She also showed, and on my first visit, all the symptoms specified by the classical school of magnetisers. On inquiry into her history—

and it is of course necessary in such a case to investigate the entire life history of the patient—I found that she had been treated many years before by a magnetiser named Perrier. In this fashion Charcot was led to reiterate, without knowing it, all the previous views of the Fluidists. To such an extent is this true that one finds almost all the special words and phrases of Charcot in the old works of the magnetisers. It was not long before Charcot found himself in controversy, particularly with the Nancy School led by Bernheim. Bernheim attributes his knowledge of method to Liébault, a medical practitioner of Nancy. The special interest of this fact is that Liébault's ideas trace back to Noizet and Bertrand. We are therefore face to face with the fact that Charcot's unwitting revival of Fluidism had led to a compensating revival of the doctrines of the Animists. The old conflict was reinstated.

It is not necessary here to consider Bernheim's contentions at length or in detail. His attitude implies a psychological explanation. His claim, briefly, is that artificial hypnosis is due to suggestion, and that Charcot's three phases are not in any sense necessary "signs," but are themselves also the product of suggestion. Bernheim succeeded finally in demonstrating his point sufficiently to throw considerable doubt on Charcot's claim—and the interest in the phenomena of hysteria declined.

This repetition of the battle between Fluidism and Animism has had very unfortunate consequences. It has had the effect of discouraging rather than encouraging research. The medical world experienced a great disappointment, since Charcot's ideas were not only easy to understand, but also seemed likely to hold the promise of further discoveries. The teaching of the Animists, on the other hand, and especially as expounded by Bernheim, was too vague for neurologists to follow. So the scientific study of the neuroses was abandoned—and the psychological phenomena considered incomprehensible.

This situation persists to the present day—neurology and psychology tread their paths alone. For so long as this continues, it is likely that we shall see the treatment of the neuroses largely abandoned to a crowd of charlatans and faddists. This has already happened here in North America. It has been responsible for the further misfortune that many of the official exponents of neurology and psychology have turned away in disgust from the study of the neuroses, instead of taking up the study where the Charcot-Bernheim controversy left it.

In spite of the general discouragement there is, nevertheless, gradually being formed an intermediary school—the medico-psychological. Certain neurologists are trying to observe more closely the early signs of mental abnormality and the physiological correlatives. The National Committee of Mental Hygiene is very properly demanding that there shall be psychopathological clinics

which shall study mental disorders in the early stages and before the sufferer has had to be incarcerated. Certain psychologists also are leaving the laboratory study of sensations to make inquiry into the various conditions of upbringing and environment which make for mental health or disability. The future, therefore, is not without hope.

An excellent illustration of the possibility of this kind of intermediary scientific study is provided by the work of the physiologist Richet. For the past forty years I too have striven in this direction —to study the psychological phenomena observed, with a view to the formulation of precise and scientific explanations. With respect to this study I cannot at this time say more than a word or two. Psychology must, of course, be an objective study just as anatomy and physiology are objective. It cannot nevertheless begin wholly outside ourselves. If "consciousness" is to be explained in precise physical terms, then it is before all things necessary that the student should pay the closest attention to what is passing in the human consciousness. If he does not do so, he is in the unfortunate position of having no precise observations with which to correlate his physical explanation when he has it. Descartes considered that thought was a primary phenomenon—"Cogito, ergo sum." As a sheer matter of fact, we know that the responses of animals, children and primitive people do not begin with thought, in the adult civilized sense, but that thought is a later development. The same assertion may be made with respect to observations of conduct or behavior. There are elementary forms of behavior, reflex and instinctive in nature, which must be carefully taken into account before the problems of highly complex behavior are investigated. Psychology, like anatomy with its divisions of spinal cord, midbrain, cortex, and so forth, has its different divisions which should have their separate terms. For example, at the bottom of the scale, one might put reflex actions, then social, intellectual, asseverative, reflective, rational and so on. In a general way, we observe that mental disease consists in a degeneration of these various forms of conduct.

I use the term moral behavior to describe the highly complex actions of civilized adults, the sum of all these elementary factors. In problems of this description, we have to remember that all men are not capable of achieving the same degree of complication in mental behavior—just as different persons require different amounts of sleep, nourishment and so on. I have myself found it profitable (in the clinic and outside it) to consider the problems of the individual from two points of view. There is always a question as to the degree of *psychological tension* an individual can achieve. There is also a *psychological quantity factor*, which conditions his capacity for social adjustment and mental development. Such studies have a practical as well as a theoretic value; they should lead to more

precise methods of psychological treatment, which I hope will not be long in forthcoming.

In conclusion, let me say that I hope that the field of the study of mental abnormalities will be reclaimed by neurology and psychology. And I hope that the study of patients will begin in clinics and psychopathic dispensaries, instead of after such patients have been incarcerated for life in an asylum.

THE EFFECTS OF ALLYL–PHENYLCINCHONIN ESTER ON METABOLISM.

By The Late Max Kahn, M.A., M.D., Ph.D.,

and

David J. Cohn, Ph.D.,

New York.

(From the Department of Laboratories, Beth Israel Hospital, New York.)

Introduction. Phenylcinchoninic acid was first synthetized by Doebner in 1887. Later it was found to possess definite physiologic action; and about twenty-five years after its first production, it was placed on the market by a German firm, under the trade name Atophan, as a remedy for gout. It was claimed that the drug had the power of inducing an increase in the elimination of uric acid. Since then a number of modifications and derivatives have been introduced to be used for similar purposes as the original product. Our present researches are primarily concerned with the allyl-phenylcinchonin ester, introduced under the designation of Atoquinol.

Phenylcinchoninic acid is a yellow, crystalline compound, melting at 209° C., and is very insoluble in water. Since its introduction there have appeared numerous clinical reports, at times conflicting in their conclusions, concerning the action of this drug. The consensus of opinion, however, appears to be that phenylcinchoninic acid (Atophan) decreases (temporarily at least) the uric acid content of the blood, and increases the elimination of uric acid in the urine.

One of the earliest comprehensive articles on the subject was contributed by Bach and Strauss, in 1912[1]. The authors treated 19 cases of arthritis urica with phenylcinchoninic acid, and made the following observations: Even on the first day, the uric-acid excretion is increased to about double of its original amount, following the administration of phenylcinchoninic acid (four doses of 0.5 gm. each, daily); the first day after the medication has been discontinued,

excretion of uric acid decreases to an amount below normal, then gradually rises again. Atophan appears to effect a lowering of the existing blood pressure. In none of the cases was an irritating effect upon the kidneys noted. In fact, 2 cases of contracted kidney tolerated the medication without ill effect, and without exhibiting chemical or microscopic changes in the urine. The subjective well-being of the patient was apparently favorably influenced in all cases; in proportion to the water intake, increased diuresis was not observed.

A. Plehn[2] reported doubling of the quantity of uric acid excreted by most individuals with chronic gout, when phenylcinchoninic acid was ingested. This increased excretion was more prolonged than in normal individuals. Plehn states that the action of the drug upon localized inflammatory conditions is very favorable, and that he never observed any untoward occurrence due to its use.

Folin and Lyman,[3] in experiments conducted with a group of 6 patients suffering from gout and with 1 person in normal health, found that, after the administration of phenylcinchoninic acid, the elimination of uric acid was increased, while the uric-acid content of the blood was simultaneously reduced. An increase in the excretion of nonprotein and urea nitrogen was also observed, leading the authors to the conclusion that the drug acts upon the kidneys rather than upon the mobilization of the urates deposited in the body.

This contention was confirmed by Skorczewski and Sohn,[4] who observed that the increase in uric-acid elimination was accompanied by chlorine retention. Eisner[5] recorded similar findings about the retention of chlorin, but he also found that the elimination of nitrogen was diminished.

In the study of exudative diathesis in children, Hans Kern[6] found that these patients eliminate exogenous uric acid less readily than do normal children. Phenylcinchoninic acid stimulated the elimination process of both endogenous and exogenous uric acid.

The amount of uric acid in the blood, according to McLester,[7] varies in different persons, but is constant for the individual. Phenylcinchoninic acid decreases this amount while increasing the uric-acid excretion. McLester believes that the drug acts upon the kidneys.

The action of phenylcinchoninic acid upon the metabolization of nucleic acid was studied by Schnittenhelm and Ullmann.[8] Gouty subjects excreted a markedly increased amount of uric acid after taking phenyl. When nucleins were fed to patients suffering from gout, the increase in the uric-acid output was smaller. In polyarthritis, neurasthenia, myelogenous leukemia, and in normal dogs, the administration of phenylcinchoninic acid together with nuclear material, increases the uric-acid elimination to a greater extent than when the drug alone is given.

Fine and Chase[9] believe that the increased elimination of uric acid and the diminished uric acid in the blood is due to increased renal permeability. They observed these manifestations experimentally as well.

Several doses (0.5 gm. each) of phenylcinchoninic acid completely clear the blood of its uric-acid content, according to the report of Frank and Pietrella.[10] After a period of two hours, a marked decrease occurs, and complete elimination takes place after twenty-four hours. The continued administration of phenylcinchoninic acid maintained this condition for weeks, but when the medication was discontinued, the uric acid quickly returned to the normal value. In cases of gout, phenylcinchoninic acid produces a considerable decrease, even down to the normal value, of the uric-acid content of the blood.

A number of observers have found that the increase in the elimination of uric acid is not absolute, but is followed by a contemporary decrease. Gries and Samson[11] find that this decrease in uric-acid excretion lasts eight to twelve hours after the maximum point of elimination is reached.

E. Starkenstein[12] arrived at the conclusion that the rise in the excretion of uric acid under the influence of phenylcinchoninic acid, when the subject is on a purin-free diet, is not due to increased formation of uric acid, because in animals, observed under similar conditions, no increase of allantoin output is observed. (Allantoin corresponds in animal metabolism to the uric acid in the human.)

In the experience of Grabfield and Pratt[13] the increase in uric acid elimination occasioned by phenylcinchoninic acid did not persist beyond the third day, and usually terminated by the second day. Contrary to the findings of previous observers, some of them quoted above, Grabfield and Pratt could adduce no evidence to the effect that phenylcinchoninic acid "sweeps out" the uric acid from the bodies of normal individuals.

From the large amount of literature on the subject, it may be gathered that, unlike other diuretics, phenylcinchoninic acid in nontoxic doses exerts no effect upon normal animals. Because this substance has no effect upon the normal or edematous organism, but seems to accentuate the diuresis already existing, it appears that, unlike most diuretics, it does not contain an extrarenal component, but a renal factor only. Independently of the diuresis present, phenylcinchoninic acid favors the elimination of uric acid and acetone; and in parallel, of chlorids and sugar. The cause of these activities can be only a stimulating effect on the secreting elements, or a paralysis of the mechanism of the inhibitory nerves.

In a recent article, Starkenstein[14] denies the allegation of a previous report by another worker that phenylcinchoninic acid causes destruction of leukocytes, but claims that there occurs a temporary paralysis of the white blood cells, without an increase in their

number, and without change in the blood circulation. The author believes that the increased elimination of uric acid is not due to destruction of leukocytes, but that the beneficial effect of phenylcinchoninic acid upon inflammatory conditions may be attributed to this paralysis of the leukocytes.

Angelina Levi[15] found also no appreciable change in the number of leukocytes.

Max Dohrn[16] produced swelling of the conjunctiva of rabbits with mustard oil, and then administered phenylcinchoninic acid, whereupon the induration became greatly diminished or abolished. His experience is that although the ethyl ester of phenylcinchoninic acid (available under the trade names of Acritin, Novatophan, Neocinchophen, Tolysin) increases the excretion of uric acid in a similar measure and as promptly as Atophan (phenylcinchoninic acid), it did not show this antiphlogistic action. The substitution of a methyl for the phenyl group of cinchoninic acids (Synthalin, Paratophan, Isatophan) deprives it both of its uric-acid eliminating and antiphlogistic properties.

The findings of Dohrn are contradicted by the work of Hanzlik and Tainter,[17] who found no antiphlogistic effect following the use of Atophan, when it was administered to rabbits with artificially induced edema of the head and neck.

In a series of experiments[18] upon a woman with gout, indications were observed that whereas lithium citrate is without effect upon the excretion of uric acid, when it is given in conjunction with phenylcinchoninic acid, the uric acid excretion is greater than when phenylcinchoninic acid is administered alone.

Quinin and phenylcinchoninic acid given together had a more powerful antiphlogistic effect upon the inflammation of the mesentery of frogs than the equivalent quantity of either of the drugs alone.[19]

Although the clinical application of phenylcinchoninic acid seems to be without untoward effect in the majority of cases, there are sporadic reports in medical literature relating unfavorable effects. E. de Oyarzabel[20] reports a case of eczema (caused by the treatment of a boil with formalin) which, due to the ingestion of Atophan, reappeared several times after healing.

A case was reported recently[21] in which the administration of Atophan was followed by severe allergic shock. According to the writer, Atophan and Novatophan are renal irritants, and after their ingestion, the urine should be watched for evidence of such irritation.

Examination of numerous reports of experimental workers with phenylcinchoninic acid and its derivatives, yields a considerable amount of more or less contradictory material, which needs to be summarized only for the purposes of this report.

According to L. Rotter,[22] phenylcinchoninic acid is decidedly

toxic to cold-blooded, but not to warm-blooded, animals. It paralyzes the central nervous system and the heart nerves of frogs. Starkenstein[23] found that dogs and cats are more susceptible to the toxic action of Atophan than frogs, mice, or rabbits. Injections of the substance into dogs or rabbits causes a temporary reduction of the blood pressure.

Max Dohrn[24] finds that phenylcinchoninic acid does not produce an absolute increase in the elimination of uric acid, but that the increased elimination is followed subsequently by lowered output, and draws the conclusion that phenylcinchoninic acid produces its initial effect by stimulating the formation of uric acid from its precursors; as the store of the latter is diminished, the output of uric acid is lowered.

Uric acid is three times more soluble in the presence of the sodium salt of phenylcinchoninic acid than in water alone.[25]

George Graham[26] avers that the additional amount of uric acid excreted under the influence of phenylcinchoninic acid cannot come from the blood, the total amount present in the blood being insufficient for this. On the other hand, he finds the evidence that uric acid deposited in the tissues can be redissolved is very doubtful.

After the administration of phenylcinchoninic acid (Atophan), Dohrn[27] isolated 8-hydroxyl, 2-phenylquinolin, 4-carbonic acid hydroxyl-atophan, hydroxyl-pyridinuric acid, and yet another unidentified pyridin compound from the urine.

Skorczewski and Sohn[28] found that when phenylcinchoninic acid is administered by mouth, the urine shows the following reactions: (1) Canary-yellow coloration with concentrated HCl; (2) yellow precipitate with phosphomolybdic acid; (3) dark green coloration on the addition of $(NH_4)_2SO_4$ and NH_4OH; (4) diazo reaction with Ehrlich's reagent.

Experimental. In connection with other studies of the clinical effects of cinchophen and its derivatives, a special study was made of the therapeutic and pharmacologic influence of the allyl-phenylcinchonin ester (issued under the name of Atoquinol) in cases of arthritis and other socalled "rheumatic" manifestations.

These studies were carried out with the following objects in view:

1. A study of the influence of the allyl-phenylcinchonin ester on the chemistry of the blood, with special reference to the uric-acid, urea-nitrogen, nonprotein-nitrogen, and creatinin contents.

2. A study of the excretion in the urine of uric acid, urea nitrogen and ammonia nitrogen, after the administration of allyl-phenylcinchonin ester.

3. Determination whether or not the compound causes renal irritation.

Blood Chemistry. Atoquinol (allyl-phenylcinchoninic acid), in doses of 0.5 gm. each, was administered to three groups of subjects, three times daily, for periods of two weeks to six weeks. The groups

of subjects were: (*a*) Normal adults, (*b*) patients suffering from arthritis rheumatica, arthritis deformans, and arthritis characterized by increased uric acidemia. Each subject was placed on a diet suitable for his case; the blood was twice examined previous to the administration of the allyl-phenylcinchonin; and further examination of the blood was made after periods of one or more days, according to indications of the individual case.

It was noticed that in all cases under observation there was a slight reduction of the hemoglobin. This was present even in 2 of the 3 normal subjects. In all the diabetic and arthritic patients there was a lowering of the hemoglobin by several degrees, as determined by the Sahli method.

The white blood cell count showed very slight variation as the result of this medication with allyl-phenylcinchonin ester. In normal subjects this drug did not cause any change in the leukocyte count. In some of the diabetic and arthritic patients a lowering of the number of white cells was observed. This was especially noted in some of the patients who had a high uric acidemia. In these cases, a lowering of the uric-acid content of the blood was, generally, attended by reduction in the leukocyte count.

The effect on the urea nitrogen and nonprotein nitrogen of the blood, was striking. In all cases there was observed a reduction in these figures. In some instances the reduction was quite marked. In certain cases, even though accompanied by renal impairment, data were recorded, indicating a lowered value of these two nitrogen fractions of the blood.

The effects on the blood creatinin were not uniform. In the 3 normal subjects, no influence whatever on the creatininemia was observed as a result of the administration of Atoquinol. In some of the patients suffering from arthritis of one type or another, who exhibited relatively high creatinin figures, together with high uric-acid values, the effect of the drug in general seemed to lower the creatinin figure to a minimum point, without, however, causing any further reduction. Thus, in case 19, there was a reduction from 2.15 mg. to 1.55 mg.; in Case 20, from 1.80 mg. to 1.35 mg. In these cases there was also observed an increased excretory renal capacity, indicated by the phenolsulphonephthalein test.

The table following shows the effect of the administration of allyl-phenylcinchoninic acid upon normal subjects.

The effect on uric acidemia was striking. As will be seen from the foregoing table, in normal subjects no lowering of the uric-acid content of the blood occurred. Neither was an appreciable influence recorded on the uric acidemia of diabetic patients, when the uric-acid content of the blood did not exceed 2 mg. per 100 cc. at the time the treatment was commenced. When, however, the uric-acid figures were above 2 mg. before the administration of the drug, the effect following the administration of this cinchonin ester brought

about a reduction in the uric acid of the blood until the optimal minimum figure was attained. Thus Case 6 showed a reduction from 4.25 mg. to 1.85 mg.; Case 9, from 4.75 mg. to 2.65 mg.; Case 13, from 5.5 mg. to 2.35 mg.; Case 18, from 6.75 mg. to 2.25 mg.; Case 21, from 5.28 mg. to 2.15 mg.*

NORMAL SUBJECTS.

Case No.	Days in relation to medication.	HGB per cent.	W. B. C. in thousands.	Urea nitrogen.	Nonprotein N.	Creatinin.	Uric acid.	Glucose.
1	Before	85	6.7	18	32	0.9	1.75	0.095
	2	87	7.4	12	25	0.8	1.85	
	4	85	7.8	14	28	0.9	1.5	
	7	80	8.2	16	28	0.9	1.65	
	9	85	7.8	12	27	0.85	1.7	0.120
	11	88	8.3	15	28	0.9	1.6	0.115
	14	86	8.4	15	25	0.85	1.6	
2	Before	92	7.3	16	25	1.1	2.05	0.110
	2	90	8.5	14	20	0.95	1.85	
	5	87	7.3	9	19	1.1	1.9	0.085
	7	90	7.4	11	20	1.0	2.0	
	9	92	7.5	11	18	1.0	1.95	
	11	90	7.5	12	20	0.95	1.8	0.112
	14	86	7.1	10	22	1.1	1.9	
3	Before	82	8.1	15	31	0.85	1.75	0.075
	3	80	8.3	12	31	0.80	1.5	
	5	78	8.4	11	24	0.8	1.65	0.090
	9	80	8.8	12	26	0.8	1.65	
	11	84	8.8	10	24	0.75	1.75	
	14	82	8.6	9	27	0.8	1.6	0.105

It is, perhaps, to be concluded from these observations that the allyl-phenylcinchonin ester does not cause a "washing out" of the uric acid that is of endogenous metabolic origin, but distinctly causes a removal of the uric acid that is in excess of the normal figure in the blood.

The allyl-phenylcinchonin ester had no effect on the glycemia in diabetic patients. The variations in the figures depended upon dietetic obedience, and the administration of insulin and intarvin to these patients.

The progress of some of the diabetic cases referred to in the foregoing discussion will be evident from the tables on page 793.

Urinary Excretory Products. A number of the patients under observation were studied with a view of determining the effects of the administration of the allyl-phenylcinchonin ester on the excretion of certain nitrogen fractions in the urine. The cases studied were 9, 13, 16, 18, and 22. The data appear on the chart on page 793.

* Roethlisberger, Valette and Roch observed similar effects in their study of this compound.

DIABETIC PATIENTS (UNDER INSULIN AND INTARVIN TREATMENT).

Case No.	Days in relation to medication.	HGB per cent	W. B. C. in thousands.	Urea nitrogen.	Nonprotein N.	Creatinin.	Uric acid.	Glucose.
6	Before	80	9.2	23	44	1.20	4.25	0.110
	2	74	7.1	18	32	1.15	3.15	0.125
	5	78	6.8	15	30	1.05	2.75	0.115
	9	76	7.5	16	34	1.12	2.85	0.118
	11	75	7.6	18	28	1.15	2.15	0.128
	15	75	7.1	15	27	1.24	1.95	0.112
	20	72	7.8	15	32	1.13	2.05	0.140
	24	72	7.4	17	28	1.12	1.85	0.114
	28	74	7.1	15	30	1.15	1.85	0.110
9	Before	78	8.8	32	57	1.45	4.75	0.165
	2	72	9.0	30	55	1.52	3.80	0.142
	6	70	8.6	27	58	1.55	3.65	0.140
	10	72	8.4	25	48	1.40	2.95	0.120
	12	70	8.5	27	54	1.50	2.75	0.112
	15	74	7.8	30	56	1.60	2.85	0.125
	18	72	8.3	32	52	1.55	2.65	0.130
	21	74	8.4	25	48	1.55	2.70	0.125
13	Before	89	7.9	18	38	1.05	5.15	0.128
	2	82	7.2	20	34	0.98	4.85	0.120
	4	85	7.8	16	36	1.15	4.15	0.124
	7	84	8.3	15	30	1.05	3.90	0.095
	9	80	8.1	16	28	1.05	3.25	0.108
	13	84	7.5	16	32	1.10	3.15	0.105
	17	82	7.8	18	32	1.00	2.75	0.112
	21	83	7.4	15	28	1.05	2.45	0.104

URINARY EXCRETION.

Case No.	Relation to medication.	Total nitrogen in gm.	Per cent urea nitrogen.	Per cent ammonia nitrogen.	Per cent uric-acid nitrogen.
9	Before	21	68.8	3.78	1.94
	6	20	72.5	5.22	2.78
	12	22	75.4	5.36	3.15
	16	21	74.6	5.12	3.22
	21	20	73.9	5.84	3.19
13	Before	18	71.5	2.94	2.12
	4	19	78.5	5.86	4.14
	9	18	79.4	5.92	3.78
	13	18	77.6	6.05	3.92
	21	18	76.9	5.27	3.88
16	Before	22	66.7	3.15	2.04
	3	21	78.4	6.22	5.17
	9	20	79.5	5.15	4.95
	18	21	81.2	5.84	4.80
	30	20	78.6	5.27	4.85
	42	20	80.5	5.65	4.76
18	Before	17	74.3	2.14	3.05
	2	16	78.7	4.32	4.32
	7	16	81.2	5.17	5.16
	14	15	80.9	5.26	5.84
	21	16	80.1	6.05	6.14
	28	16	79.9	5.84	5.24
22	Before	19	71.4	3.78	2.75
	2	20	76.3	6.18	4.14
	10	18	77.8	5.94	4.08
	15	18	76.9	5.85	5.15
	21	19	76.6	6.05	4.86
	28	18	77.5	5.74	4.82

It will be seen that, as the result of the administration of this cinchonin ester, there appeared in the urine an increased elimination, both relative and absolute, of the uric-acid nitrogen, urea nitrogen, and ammonia nitrogen.

It can be stated definitely that the administration of allyl-phenyl-cinchonin ester (Atoquinol) does not produce renal irritation. As regards the excretion of phenolsulphonephthalein, it was observed that after the administration of this drug for several weeks, there occurs no lowering in the phthalein output, but, on the contrary, a definitely increased output of phthalein is observed.

Conclusions. 1. The administration of allyl-phenylcinchonin ester (Atoquinol) causes no gastric irritation.

2. It causes a decrease in the uric acid of the blood, as well as a reduction of the nonprotein nitrogen of the blood.

3. It produces an increased output of uric acid in the urine.

4. It occasions no renal irritation.

The table appended shows the effect of allyl-phenylcinchonin ester on the condition of some of the patients suffering from arthritis, who were the subjects of these observations.

ARTHRITIC PATIENTS (NONDIABETIC).

Case No.	Days in relation to medication.	HBG per cent.	W. B. C. in thousands.	Urea nitrogen.	Nonprotein N.	Creatinin.	Uric acid.	Remarks.
15	Before	65	5.8	34	58	1.80	4.75	Albumin.
	3	65	5.9	32	56	1.60	4.50	Hyaline casts.
	6	68	6.1	24	60	1.60	4.15	
	9	65	6.2	26	52	1.70	3.80	
	15	64	6.1	24	48	1.65	3.65	P.S.P. before total 52 per cent.
	19	70	5.8	25	42	1.75	3.20	
	24	68	5.7	22	48	1.65	2.75	
	29	68	5.6	19	36	1.70	2.80	P.S.P. after five weeks total 60 per cent.
	35	68	5.9	24	34	1.85	2.50	
16	Before	82	8.6	29	62	1.48	4.45	P.S.P. before total 45 per cent.
	1	84	8.6	25	54	1.40	4.10	
	3	80	7.8	24	48	1.40	3.15	
	7	78	7.5	18	52	1.30	3.05	
	9	78	6.9	25	37	1.25	2.65	
	12	76	7.8	18	42	1.35	2.65	
	18	78	7.5	16	30	1.35	2.25	
	24	74	7.6	19	34	1.40	2.25	P.S.P. after five weeks total 58 per cent.
	30	78	8.1	20	42	1.35	2.35	
	35	75	8.4	18	32	1.38	2.15	
	42	75	8.5	20	34	1.35	2.20	
17	Before	78	9.3	28	52	1.15	4.80	P.S.P. before total 53 per cent.
	2	76	8.8	26	48	1.10	4.15	
	4	74	8.5	24	50	1.15	4.20	
	7	75	8.4	20	42	1.05	3.20	
	11	75	7.3	20	42	1.05	2.35	
	15	74	8.5	22	44	1.10	2.40	
	18	75	7.2	20	37	1.08	2.85	
	24	72	7.4	18	34	1.10	2.20	P.S.P. after four weeks total 68 per cent.
	28	75	6.9	20	35	1.05	2.15	
	31	75	7.4	22	36	1.05	2.40	
	35	74	7.2	16	28	1.00	2.25	

ARTHRITIC PATIENTS.

Case No.	Days in relation to medication.	HGB per cent.	W. B. C. in thousands.	Urea nitrogen.	Nonprotein N.	Creatinin.	Uric acid.	Remarks.
18	Before	84	8.8	17	39	1.05	6.75	"Gouty" arthritis.
	2	80	...	17	35	1.05	6.10	
	5	78	...	16	30	0.95	5.15	
	7	76	...	12	28	....	3.85	
	9	75	8.2	15	32	1.05	4.05	
	14	74	...	14	34	....	3.50	
	17	76	...	17	28	1.15	3.10	
	21	74	7.5	16	24	1.05	2.85	
	24	75	7.4	14	26	1.00	2.60	
	28	74	...	12	25	1.05	2.35	
	31	76	8.2	15	24	1.10	2.25	
19	Before	76	9.2	37	68	2.15	4.15	P.S.P. before total 37 per cent.
	2	74	8.1	35	70	1.85	3.20	
	5	72	8.4	28	62	1.65	3.25	
	9	74	...	30	60	1.45	2.80	
	11	75	8.2	24	52	1.55	2.45	
	14	75	...	22	44	1.45	2.50	
	17	72	8.0	22	40	1.45	2.15	
	22	74	...	18	38	1.45	1.85	P.S.P. after four weeks total 58 per cent.
	25	70	7.8	18	32	1.50	2.20	
	28	72	8.3	20	35	1.35	2.10	
20	Before	88	6.9	31	55	1.80	3.95	P.S.P. before total 55 per cent.
	2	84	7.1	24	50	1.75	3.60	
	4	85	6.8	26	50	1.50	3.15	
	7	82	6.5	22	40	1.65	2.75	
	11	80	7.3	24	42	1.45	2.80	
	14	82	...	22	38	1.55	2.45	
	17	84	7.5	23	38	1.50	2.15	P.S.P. after three weeks total 56 per cent.
	21	85	...	19	32	1.35	2.25	
	25	82	7.4	20	40	1.55	2.05	

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THE IMPORTANCE OF UROLOGIC DIAGNOSIS IN INTERNAL MEDICINE.

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Tolstoi, who did not have much esteem for the medical profession in general, once remarked that there are only two kinds of doctors: The conservative, who lets his patients die, and the radical, who kills them. Sir William Osler, paraphrasing this remark, stated: There are only two sorts of doctors—those who practise with their brains, and those who practise with their tongues. Both these renowned men recognized the fact that medicine is not always practised in the ideal way, which is no doubt due to a lack of balance or coördination in the methods employed and the manner of their administration by different physicians. In presenting this paper, we hope we shall not be regarded as too conservative nor too radical, and prove the point we wish to stress to be based on a careful and systematic study of a group of cases in which the facts have been clinically and scientifically demonstrated.

The term internal medicine does not represent a new field in medical science. It is merely a modern appellation to one of the most ancient departments of medicine. It has, however, a newer meaning and broader significance on account of many recent discoveries and achievements, so that it now embraces all the domains of the various medical specialties. Among these may be mentioned neurology, gastroenterology, cardiology, urology, laryngology, ophthalmology, dermatology, endocrinology, etc., besides certain laboratory procedures, including roentgenology, bacteriology, serology, parasitology and the chemistry and morphology of the blood, spinal fluid, urine, feces, etc. These various domains are so closely interrelated anatomically and physiologically, and so interdependent functionally that it is impossible to exclude any one of them in making a clinical investigation without menacing the opportunity of arriving at a complete and accurate diagnosis.

Some of these domains have been sufficiently stressed, while others have been sorely neglected. This neglect cannot always be ascribed to ignorance. Esthetic tendencies on the part of the physician may prevent him from making the necessary digital examinations of the rectum or examining the stools of his patients, while on the other hand the financial circumstances of the patient may not permit an extensive roentgenologic study or a complete investigation of the urogenital tract. Nevertheless, it is an

undoubted fact that these measures are equally as important as feeling the pulse, looking at the tongue or listening to the heart. Since facilities have been amply provided at our clinic for a complete urologic study of patients, whatever their circumstances may be and whenever indicated, the incidence of this class of diseases, according to our records has more than doubled. This implies that hitherto, by error of omission, we actually failed in making a proper diagnosis in more than 50 per cent of the cases. Our only consolation resides in the fact that nearly all of the patients had previously been in the hands of capable physicians, who likewise failed to recognize the true nature of their malady.

Patients with urologic diseases, who present themselves for diagnosis at a medical clinic, usually do not suspect a lesion of the urogenital tract. This largely accounts for the frequency with which they have been encountered in our practice. Their symptoms are often referred to some other domain, such as the gastrointestinal, neuromuscular or cardiovascular system. If they should suspect the primary seat of their disease they would either personally seek the advice of a urologist or be referred to one by their attending physician.

In reviewing our cases those with obvious lesions of the genitalia in the male, such as urethritis, stricture, prostatitis and epididymitis and lesions of the reproductive organs in the female, such as uterine, ovarian, tubal and vaginal diseases, as well as nephritis in all its forms, have been omitted. Only those cases presenting diagnostic difficulties or requiring special urologic investigations have been included. While the general rule was not to examine every patient urologically who came to the clinic, certain definite types of cases were investigated.

These, for the purpose of discussion may be divided into two main groups: (1) *Patients having definite urologic signs, symptoms or both, associated with other conditions;* (2) *patients having indefinite complaints not directly associated with the urogenital tract, in which a satisfactory diagnosis could not be made without a urologic study.*

In the first group there were 20 cases with definite urologic signs, 21 with definite urologic symptoms and 41 with both signs and symptoms.

In the second group there were 40 cases, or 32.8 per cent. This was the perplexing group. In 35 of these cases definite urologic pathologic lesions were found. These included: Pyonephrosis, 1; pyelonephritis and pyelitis, 4; renal calculi, 3; hydronephrosis, 4; nephroptosis, 2; hydroureter, 2; anomalies, horse-shoe kidney, 1; double pelves and ureters, 5; ureteral stricture, 14; ureteral kink, 1; ureteral spasm, 1; vesicle neoplasm, 1; trigonitis, 2; tabetic bladder, 1; prostatitis, 5; urethritis, 4; urethral stricture, 1; veru montanitis, 3; spermatocele, 1. There were only 5 cases in which no demonstrable urologic lesion was found.

The symptoms in this group were referred chiefly to the gastrointestinal, neuromuscular, cardiovascular and endocrine systems.

Gastrointestinal symptoms, for which these patients sought relief, dominated the clinical picture in 18, or 45 per cent, of the cases. Ten complained of periodic nausea and vomiting. Other symptoms present were epigastric pressure, general or local abdominal pains, eructation, pyrosis, constipation, etc. Thorough gastrointestinal investigation, including Roentgen ray, failed to reveal any gross anatomic lesions which could account for the symptomatology, except in 2 cases in which the diagnosis of gall stones was made. Two of the patients had gastroenteroptosis. The reflex gastric disturbances in 11 cases were apparently due to lesions of the kidneys or ureters. Three suffered from renal calculi, 4 from pyelitis and 14 from ureteral strictures.

The chief complaints of 9 patients in this group were of neuromuscular origin, either in the form of a psychoneurasthenic state or local or general muscular pains. One of these patients was a miserable sufferer for eighteen years on account of persistent ill-defined and shifting pains. They had been described at various times as intercostal, pleural, precordial, lumbar, sciatic, abdominal, appendiceal, and menstrual; about as many diagnoses had been made. In fact, she had her appendix removed at one time and at another the uterus dilated and curetted without any relief. The urologic examination revealed the presence of an anomaly of the left kidney with two pelves and two ureters, with stricture and hydronephrosis in one. By means of repeated dilatation of this ureter most of her pain subsided, and for the first time in many years she has been able to abandon the use of anodynes and narcotics.

There were only 2 cases associated with cardiovascular symptoms; both were luetic. The diagnosis of a tabetic bladder was made in both.

In 3 cases symptoms of myxedema masked the urologic condition of the patient. One suffered from renal calculi, 1 from ureteral stricture and 1 from veru montanitis. Hypothyroidism is known to predispose to urologic lesions of this character.

In considering the two groups mentioned collectively, it is remarkable to note the number and variety of diseases encountered. They comprise almost every type one may expect to find in the urologic tract, and in many instances several conditions were associated. Thus there were 61 lesions of the kidneys, 45 of the ureters, 34 of the bladder, 22 of the prostate, 3 of the seminal vesicles, 34 of the urethra and 7 of the scrotum, making a total of 206 lesions.

Diseases of the Kidneys. In order of frequency pyelitis and pyelonephritis rank first, numbering 25. This was followed by hydronephrosis, 9; anomalies, 8; nephrolithiasis, 6; neoplasm, 5; pyonephrosis, 4. Three cases of pyelitis simulated so closely other conditions that they were erroneously diagnosed (1 as typhoid fever,

1 as rheumatic fever and 1 as postcecal appendicitis), while, on the other hand, through secondary invasion infectious polyarthritis occurred in 3 cases and multiple neuritis in 2 cases. The source of infection in all of these cases had not been ascertained prior to our investigation. Chronic infection of a focal character almost invariable coëxisted. The most constant were infected tonsils, alveolar abscesses and paranasal sinus infection. Cholecystitis, influenza and syphilis respectively appeared as factors in 3 cases.

The presence and degree of hydronephrosis associated with ureteral stricture depended upon the degree and chronicity of the condition.

We were rather startled to find the incidence of congenital anomalies of the kidney to exceed those of renal calculi in our studies. This is certainly not the usual finding. However, it emphasizes the importance of the subject as one which should not be neglected. To the group of anomalies belong 1 horse-shoe kidney; 1 congenital absence of the left kidney; 6 double pelves with double ureters, 5 occurring on the left and 1 on the right side.

The neoplasms consisted of 1 carcinoma of the renal pelvis and calyces and 4 hypernephromas. One of the patients suffering with pyonephrosis had been diagnosed appendicitis, and had the appendix removed without relief of symptoms or suspecting any lesion of the kidney. Another was being treated for a dermatitis.

Diseases of the Ureters. The lesions of the ureters consisted of strictures, 30; hydroureters, 12; calculi, 7; kinks, 2; anomalies, 7. Of the 30 strictures, 9 were associated with hydronephrosis, 12 with hydroureter and 25 with pyelitis. Four occurred in congenital extra ureters, 19 affected the left side and 11 the right side. Focal infection seems to play the same role in this group as it does in the pyelitic, except in the congenital forms in which they were absent.

In the absence of pyelitis ureteral strictures are frequently diagnosed appendicitis and the patient subjected to needless surgery. This happened in 4 of our series. There were also 2 dilatations and curettments and 1 cervical amputation without benefit to the patient. Clinical experiences of this kind are encountered by all physicians who thoroughly study their cases; therefore we wish to sound a note of warning to those who fail to do so, and to the surgeons who are ever ready and eager to operate without the proper scientific investigation. It is not the stricture that gives rise to the symptoms which are frequently obscure and misleading, but the increased intrarenal pressure, due to a beginning or definite hydronephrosis or a secondary infection in the nature of a pyelitis.

There were 7 cases of ureteral calculi. These mechanically produced the same effect and consequently the same symptoms as ureteral stricture. In addition, however, there was usually a history of acute attacks of pain occurring periodically and frequently radiating and red blood cells in the urine.

Diseases of the Bladder, Prostate and Urethra. These included: Calculi, 3; cystitis, 7; trigonitis, 4; neoplasm, 5; diverticula, 2; tabetic bladder, 2; congenital urethral stricture, 3; veru montanitis, 12; urethritis, 9; urethral caruncle, 3; urethral papilloma, 1; urethral anomaly, 1; a total of 52.

Trigonitis and veru montanitis were by far the most common, comprising 40 per cent of the total. Two factors stood out prominently in these cases, namely, the majority suffered with various sorts of neuroses, especially sexual neurasthenia, and in almost every instance they were accompanied by focal infection in the tonsils, teeth or sinuses.

The neoplasms consisted of 2 infiltrating carcinomas and 3 malignant papillomas.

A diagnosis of tabes dorsalis was confirmed in several of the patients by a cystoscopic examination. Fourteen cases of hypertrophy of the prostate occurred in this series, 1 of which was malignant, and 8 cases of prostatitis. In the latter the constitutional symptoms were due to the focal infection. All acute venereal diseases were excluded.

As the primary object in presenting this paper is to emphasize the importance of recognizing urologic lesions as they pertain to internal medicine, we hope we may be pardoned for citing so many figures. However, without them we would have failed to point out the relative frequency as compared to lesions affecting other domains. As stated in the beginning, we feel that the entire subject does not receive the attention it deserves. Certainly in our clinic we failed to do justice until we became awakened to the fact that we were actually neglecting it.

Diagnosis. In order to avoid the pitfalls alluded to, one must establish a thoroughly systematic routine for the study of all chronic cases. The commonest error made, that of not examining the urine of every patient, both chemically and microscopically, is almost inexcusable. The chemical analysis is of the greatest importance in diagnosing extraurogenital diseases and the various forms of nephroses, but it is of comparatively little value in diagnosing any of the numerous lesions mentioned in this paper. The microscopic examination of freshly voided urine, however, is very essential. The presence of pus cells should always make one suspicious of a urinary lesion. Whenever they are found repeated examinations should be made, and in women freshly catheterized specimens should be obtained. If pus cells are persistently present a cystoscopic examination should be made.

In cases of pyuria, especially if the pus comes from the ureters, cultures should be made in order to ascertain the nature of the infection. The presence of red blood cells in the urine is even more significant. Their appearance is always pathologic, and in the absence of large amounts of albumin or casts betokens some lesion

in the urogenital tract, such as calculus, infected hydronephrosis, tuberculosis or malignant neoplasm.

Pus or red blood cells in variable amounts furnished a clue to a diagnosis in fully 50 per cent of the cases.

The history of the patient, especially in regard to pain and bladder function, while extremely important, is often misleading. Dysuria, nocturia and pollakiuria may be due to pelvic pressure, such as uterine fibroids, retroversion, pelvic abscesses or the relaxation of the pelvic outlet with uterine prolapse, cystocele, and so forth. Again, it may be due to nephritis, diabetes, nervous irritability, cord lesion or myxedema. It must be borne in mind that it is possible to have definite lesions of the kidneys or ureters in individuals who manifest no symptoms referable to the urinary function and whose urine is persistently free from any pathologic elements. The following case is cited as an illustration.

A young marine engineer enjoyed perfect health until two years previous, when he began to suffer with pain in his back. This pain was his only symptom. It gradually became worse and at times disabling. During the two years he sought advice in many of the best clinics in the world. The urine was always reported normal, and he never suffered from any disturbance of micturition. On examination he did not present any evidence of a functional neurosis and showed no physical signs of any organic disease. However, a cystoscopic and pyelographic examination revealed a double pelvis and two ureters on the left side with a stricture in one ureter, which was accompanied by hydronephrosis. The pain promptly subsided after dilatation.

Technique of Urologic Examination. After a complete physical examination is made which includes routinely a chemical and microscopic examination of the urine and a blood Wassermann, a combined phthalein test is made to establish the renal function and a microscopic reëxamination is made of the urine for blood, pus and casts. In female patients a catheterized specimen is obtained for the purpose. In the male the prostate is massaged and the secretion expressed is examined microscopically.

During the cystoscopic examination any anatomic abnormality or pathology in the bladder is noted, particular attention being paid to residual urine, capacity of the bladder and in the female to the presence or absence of caruncles. Before examining the ureters the orifices are observed, noting the type of opening and the number. If in doubt as to an extraureteral orifice, indigo carmin is given intravenously and the blue spurts watched for carefully. Both ureters are always examined for the first time with a No. 9 wax bulb to determine whether a nonradiable calculus or a stricture is present. Urine is collected from both kidneys and examined microscopically. Urine from the kidneys should be cultured, and when considered necessary guinea pigs inoculated. Separate phtha-

leins from each kidney should be made, especially if an operation on the kidneys is considered. One kidney at a time is pyelographed, always determining the capacity with water and injecting 2 cc. less than the capacity of 13.5 per cent solution of sodium iodide with the tip of the catheter low in the ureter or withdrawn entirely after the injection.

The interpretation of the ureteropyelograms is of utmost importance and should be made by the urologist, independent of the roentgenologist.

Treatment. The line of treatment instituted varied from massage of the prostate, application to the veru montanum and irrigation of the bladder to intraureteral manipulation and open operation. These may be divided as follows:

1. Cases in which an open urologic operation was performed, 20 (16.39 per cent).
2. Cases in which other operations were necessary, 6 (4.9 per cent).
3. Cases which were treated by urethroscopic, cystoscopic or intraureteral manipulations, 54 (44.26 per cent).
4. Cases in which other forms of treatment were applied, 49 (23.45 per cent).

In this series there were 122 urologic cases which represent approximately 7 per cent of the cases admitted to the clinic for diagnosis. The results of treatment were as follows:

	No.	Per cent.
Cured	34	27.9
Improved	46	37.7
Unimproved	27	22.1
Still under treatment	10	8.2
Died	5	4.1
Total	122	100.0

An analysis of the study of these cases emphasizes certain definite points for consideration. In the first place it stresses the importance of taking a careful urologic history as a routine in clinical diagnosis. Such symptoms as nocturia, polyuria, dysuria and pollakiuria are all significant and often diagnostic. However, of greater significance is the presence of pain. The character, location, radiation and relation to posture and urinary function of subjective painful sensation must be determined. Tenderness or painful pressure points must also be ascertained on physical examination. The most important of these are the posterior lumbar (kidney) suprapubic (bladder), rectal on digital examination (prostate)—vaginal iliac and paraumbilical—ureteral stricture and pyelitis. The tender areas in the iliac regions known as Morris' point is well known. Recently Dr. John E. Legge described a similar point of tenderness definitely localized and circumscribed about 2 cm. laterally from

the umbilicus. This point is present in practically all patients suffering with ureteral stricture and its sequelæ. It has the advantage over Morris' point in that it does not lead to confusion with McBurney's point if the lesion is on the right side.

The urinary findings are often not dependable as gross anatomical lesions frequently occur without any chemical and microscopic evidence in the urine.

Another important point in this analysis is the fact that the reflex disturbances, especially the gastrointestinal, so completely dominate the clinical picture that the urologic nature of the disease may be entirely overlooked. The effect of the urologic lesions upon the general nervous system producing neurasthenia and psychothenic states are equally misleading.

Conclusion. 1. Seven per cent of cases admitted to the medical clinic for diagnosis were of a urologic nature.

2. Patients suffering with urogenital diseases who apply for treatment at a medical clinic are frequently not diagnosed as such.

3. Internists should either provide for proper facilities for the study of these cases or refer them to a urologist for diagnosis.

4. A systematic routine should be adopted by all practising physicians for the investigation of chronic diseases which should include a microscopic examination of the urine in every patient.

5. Reflex disturbance from the kidneys, ureters and bladder, especially of the stomach, frequently lead to error in diagnosis.

6. Gross anatomic lesions of the kidneys and ureters may exist without giving rise to any functional disturbance of the bladder or any pathologic findings in the urine.

7. A certain group of chronic medical patients in which all treatment had failed resulted in either absolute cure or definite improvement in 65 per cent after treatment was established on a urologic diagnosis.

8. Many patients are allowed to suffer because of lack of coöperation between the surgeon and internist as well as the urologist and internist.

STUDIES IN HUMAN CONSTITUTION—NO. IV.

HEREDITY AND ENVIRONMENT—THE DISEASE MAKERS.*

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HERBERT SPENCER[1] defined life as being the continuous adjustment of internal to external relations. Had he extended this

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thought for the benefit of physicians, he might well have added the corollary that disease was the declaration of a maladjustment of these forces. Among its external relations the universe supplies not only sustenance and other vital needs of the living organisms, but also directs injurious pressures upon them. These pressures may be physical in nature, or chemical, or bacterial, or psychic. The more obvious and violent a pressure becomes, and consequently the more difficult to resist, the simpler it is to look upon it as the cause of the afflicted organism's distress. The great work of Pasteur and Emil Fischer, demonstrating two vast forces in man's external relations, turned medical thought hopefully to the study of environment. But though for the past three-quarters of a century the adverse forces of the universe have received perhaps the chief attention of inquiring medical thought, there have been many eager students of man's internal relations—that other necessary factor in the production of disease. Clearly then, diseases are essentially sets of observable phenomena which recur with sufficient regularity to form entities for the physician. Their symptoms and signs express the conflict between the unique inherent "internal relations" of the individual and the intrinsic "external relations" of his particular environment. With the latter we are concerned only as they may from time to time influence the individual. Our main interest is with the study of the individual's "internal relations"—his constitution. The definition which we have used as a working basis at the Constitution Clinic at the Presbyterian Hospital is this: "Constitution is that aggregate of hereditary characters, more or less influenced by environment, which determines the individual's reaction, successful or unsuccessful, to the stress of environment." If the content of this definition be laid out broadly and completely it truly sets a Herculean task for the student of constitution. Yet it is properly our task, for the patient who consults a physician inevitably presents this trinity of problems—the disease process, the malevolent external agent and the man himself.

What, then, is the man himself? At least he is something which has passed through a stage of growth and development. But it is hard to conceive that simply the provision of nutriment accounts for growth and development. Obviously without nourishment these phenomena would not take place. But there is something inherent in the animal cells which drives them to divide, multiply and differentiate into special organs. Food alone cannot be presumed to do more than make possible the achievement of what may be called cell purposes. Furthermore, while food continues to be taken throughout life growth, from the standpoint of augmentation in size or the building of other special organs, comes to a stop when maturity is reached. Yet while growth in the sense of augmentation ceases, cellular proliferation for purposes of replace-

ment continues until the death of the whole organism. It is also true that throughout the growth and development stage, which is characterized by the most violent production of new tissue, necrobiotic processes are actively going on.[2] But during this period there is a great preponderance of viabiotic over necrobiotic activity. Perhaps the course of life is roughly marked off into three epochs determined by the changing relationships of viabiotic to necrobiotic forces. Now the capacity which cells possess of growing and developing in a fashion characteristic of a given species are laid down in the genetic plan and, so far as we know now, are passed on through the medium of the chromosomes. But adverse as well as useful environmental forces from the first play upon the new organism and immediately modify its character. Thus two sets of agencies are continuously at work modeling and remodeling the individual. Consequently, at any given moment in its life the thing which appears, the phenotype, is the up-to-the-instant result of hereditary forces distorted by environmental pressure. The first of these influences is known technically as idiokinetic, the latter as parakinetic.

From the purely objective standpoint the study of this "up-to-the-instant" specimen can be of the greatest usefulness and interest. This is the sort of study which for a long time lost caste because of the charlatanistic tendencies of certain phrenologists. But Cuvier,[3] Blumenbach,[4] Lavater,[5] John Hunter,[6] Darwin,[7] Galton,[8] Addison,[9] Laycock,[10] Hutchinson,[11] di Giovanni,[12] Bryant,[13] Bean[14] and a host of others in the past have made invaluable contributions to the knowledge of the qualities of human beings. More recently, Martius,[15] Krause,[16] Julius Bauer,[17] Davenport[18] and Viola[19] have made important additions to the previous literature of the subject of human constitution. In the Constitution Clinic at the Presbyterian Hospital we have been working on a technique for the objective study of the phenotype. In the general plan of this work the total personality was divided into four panels—anatomic, physiologic, psychologic and immunologic.[20] Furthermore, human beings were classified according to their disease potentialities. But it is not a recapitulation of these already reported objective studies of the phenotype's constitution which is the purpose of this communication. Rather it is a discussion of two or three examples of attempts to study the mechanism which has produced the phenotype.

In the anatomic panel a striking example of a modifying parakinetic influence is to be found in the effect of castration upon the long bone growth. Tandler and Gross[21] reported that in the religious sect of the Skopsi, where youthful mutilations were practised, the castrates were larger than the average of their race. Several years ago I[22] reported the case of an individual who had grown 6 inches in height within a few months following a destruc-

tive orchitis due to mumps. In the physiologic panel one has only to mention malnutrition in early youth to call to mind the great variety of inadequate constitutional states which depend largely on the adverse parakinetic influence of insufficient or improper food. But the parakinetic influences which have seemed to us recently to be of especial interest, and which may be subversive of the genetic plan, are those which act upon the psychic panel. The difficulty of dealing with this aspect of the study of constitution is very great, because as yet there are no true tests of psychic reactions. Furthermore, there is reason to believe that the endocrine glands, which exert such important effects upon growth, are directly influenced by emotional stimuli. Consequently, to the elucidation of these psychophysiologic phenomena we can bring little better than empirical beliefs. However, these empirical beliefs are built upon clinical observations and correlations which are so suggestive as to warrant further thought and investigation.

There is no longer any question that the gonads, pituitary and thyroid glands are definitely involved in the phenomena of growth and development. The relationship of the adrenal to the self-preservative mechanism is also well known. Furthermore, it is now generally recognized that any of the emotions concerned with self-preservation or perpetuation can produce profound physiologic effects. Indeed, under a terrific fear emotion, the transient picture of Graves' disease may arise. What then may be the effect of fear established in childhood and acting continuously through subsequent years, below the level of conscious consciousness, upon the thyroid's influence in the growth process? Obviously, the effect will differ in each individual, depending on the other factor, his inherited constitution. Thus similar fears will affect one person differently from another, just as similar chemicals or bacteria will affect different individuals differently. Furthermore, it is interesting to observe that patients suffering from chronic fear find their way either to the endocrinologist or the psychiatrist, for they are generally diagnosed as an endocrine unbalance or a neurosis.

In this connection, it may be of interest to cite 2 cases which illustrate the effects of parakinetic forces and 2 cases which illustrate that of the idiokinetic. In each one of the first pair the shocking death by suicide of the father during the patient's childhood occurred.

In one case a woman, aged thirty-four years, presented herself with tremor, rapid pulse, mild exophthalmos and a swollen thyroid. At the age of eight years she had stumbled over her father's body in the dark, and her hands, thrust out to break her fall, plunged into the pool of blood from his cut throat, and the light turned on at that moment disclosed the gaping wound in his neck. This ghastly memory never left her and completely outweighed and obliterated her very terrible war experiences in France, which

ended in the blowing to pieces of her fiancé at Ypres. But this patient's mother had a small tumor of the thyroid and her siblings were thin and tall. Possibly further evidence of her bad glandular heritage, if not the effect of the shock, was the history of menstrual onset delayed until the seventeenth year.

The second case was that of a man, aged forty-eight years, who had complained of chronic indigestion and finally developed an ulcer of the stomach. In early youth this patient had lived in great luxury, but when the father shot himself there followed a humiliating disclosure of mismanagement and misuse of funds. The result necessitated complete change in the youth's mode of life, and then came years of misery for an exceedingly proud spirit. He dropped his friends lest they should drop him, and became a recluse. Unlike the first case, this patient's family showed no glandular dyscrasias. His pulse rate was 66 and he was well nourished, but he was always easily fatigued.

If these emotional experiences are sufficiently potent to be accepted as playing some part in the causation of the diseases of these 2 patients, it is logical to ascribe to them also parakinetic values in the production of modified constitutions. Possibly of the same nature as these, but less spectacular, are the cases of 5 or 6 school boys, whose despairing mothers brought their sons consecutively, each with the same question, "Doctor, won't you give my boy some glands to make him concentrate?" The boys were all at the moment overgrown, had low blood pressure and complained of constant fatigue and indigestion. In every case a history was obtained telling of constant criticism and reproach by parents and schoolmasters for not doing better work. As far back as they could remember they had been told they were no good, inadequate or failures. Thus they all suffered from a profound inferiority sense, a definite form of fear, at a time of life when the endocrine glands were especially concerned with the growth process and the establishment of sexual maturity. It is not difficult to believe that the direction of the idiokinetic forces may be deflected at this stage by the impact of such a profound emotional disturbance.

It is, of course, much easier to study the parakinetic influences involved in the production of a given phenotype than it is to demonstrate the idiokinetic. For really successful display, the latter require a reliable history of the patient's family tree—at least as good a one as those kept for prize cattle and race horses. Davenport, in the Eugenics Record Office, and Karl Pearson,[23] in the *Treasury of Human Inheritance*, have collected a mass of genetic material, but they both bear witness to the obstructions raised by public ignorance and fear which leads to secrecy and inaccuracy of memory. Nevertheless, it is possible now and then to secure a dependable genealogic chart which shows the constantly reappearing of Achilles' heel of an inherited susceptibility. For some time

now at the Constitution Clinic we have been collecting pedigrees in order to trace out these idiokinetic factors as part of our technique for the study of constitution. The first example is that of a woman, aged sixty-three years, who came to the hospital because of dia-

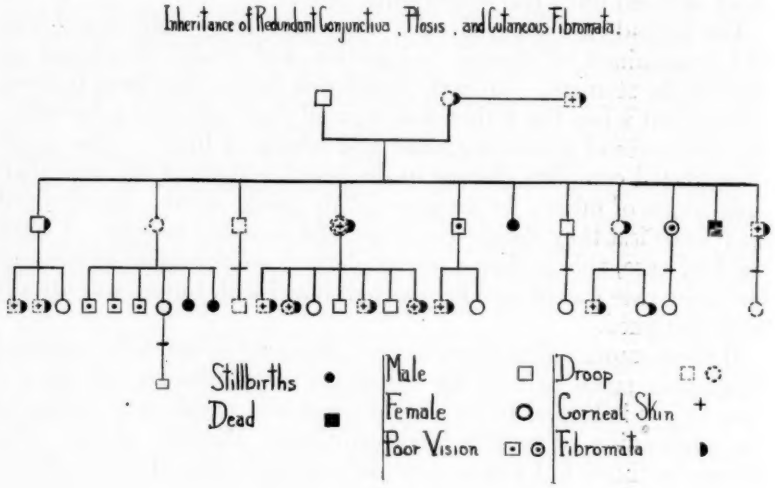

FIG. 1

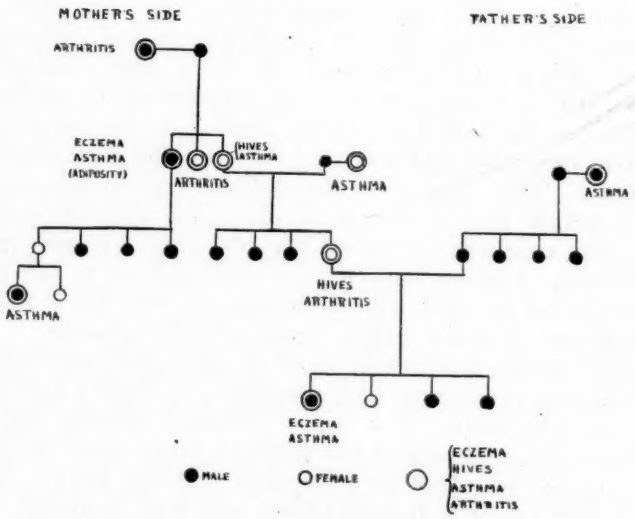

FIG. 2

betes. She had, in addition, double ptosis of the eyelids, subcutaneous fibromata and a curious redundancy of the conjunctiva. These three characters were found to exist in practically every member of her very large family (Fig. 1). There is very little

doubt that we are dealing here with an inherited fault in mesodermal tissue which appears to be a dominant character. Pancreas, likewise, having certain mesodermal associations, the possibility of an important relationship in family diabetes suggests itself.

The next example is of a family in which sensitization phenomena appear with great frequency in the form of eczema, hives, asthma and chronic rheumatism (rheumatoid arthritis) (Fig. 2).

These qualities appear to be recessive inheritances. It is interesting to observe that this chart was made in the course of a study of rheumatoid arthritis. Precisely similar charts were shown by Addison,[24] of Boston, in a discussion of the genetics of asthma. This rather suggests that the conditions mentioned are merely varied expressions of the same basic process of hypersensitization.

Finally, the demonstration of the idiokinetic factor is seen in this series of 50 families with acute rheumatic fever (Fig. 3 and Tables I, II and III).

TABLE I.—INFLUENCE OF HEREDITY IN ACUTE RHEUMATIC FEVER.

Father. ♂		Mother. ♀	Sons. Negative.	Sons. Affected.	Daughters. Negative.	Daughters. Affected.	Totals.
+	×	+	6	2	7	9	24
0	×	+	24	19	19	15	77
+	×	0	19	5	22	13	59
0	×	0	19	11	30	14	74
Totals, negative or affected			68	37	78	51	
Grand total of offspring			105		129		

TABLE II.—INFLUENCE OF HEREDITY IN ACUTE RHEUMATIC FEVER.

Father. ♂		Mother. ♀	Percentage of total affected sons or daughters in each parent combination. ♂	♀
+	×	+	18.1	17.6
0	×	+	51.3	29.4
+	×	0	13.5	25.4
0	×	0	29.7	27.4

TABLE III.—INFLUENCE OF HEREDITY IN ACUTE RHEUMATIC FEVER.

Percentage totals of all affected offspring in each parent combination. Sex, ♂.		Sex, ♀.	Per cent.	Percentage of affected sons and daughters from each parent combination. Sex, ♂.	Sex, ♀.
+	×	+	45.8	25.0	56.0
0	×	+	44.1	44.2	44.1
+	×	0	30.5	20.4	37.1
0	×	0	33.7	36.7	31.8

The material consists of 50 families, including several in which three generations are recorded. If the second generation of each of these be looked upon as a separate family, then we can report a total of 60 families with 234 offspring.

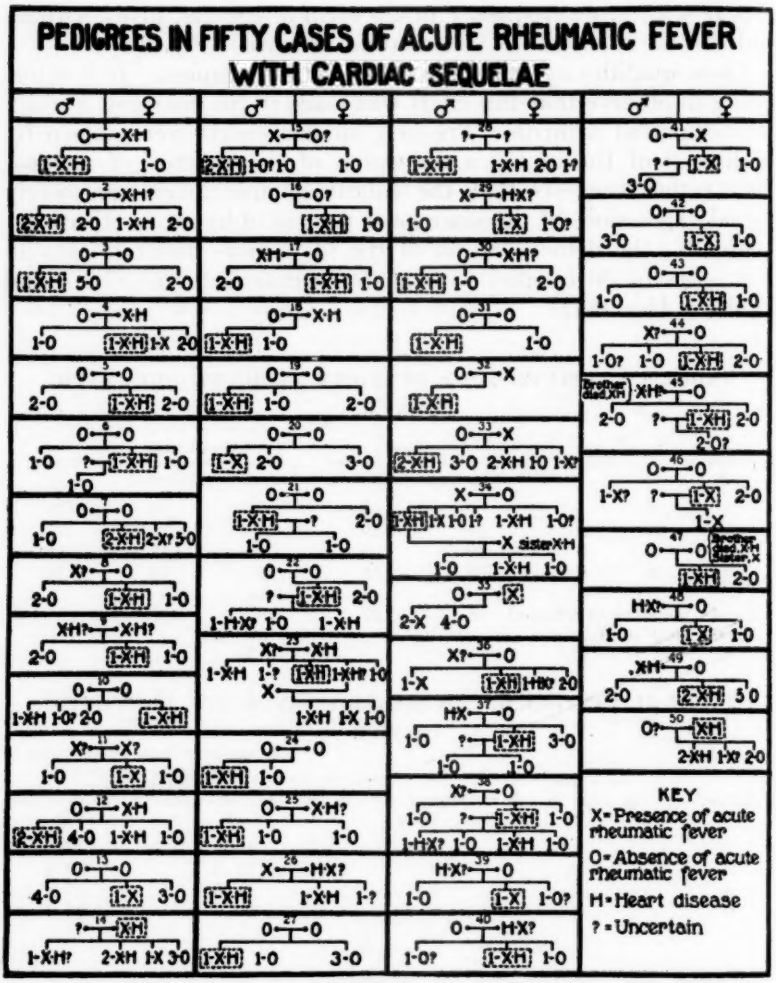
PEDIGREES IN FIFTY CASES OF ACUTE RHEUMATIC FEVER
WITH CARDIAC SEQUELAE
KEY
X = Presence of acute rheumatic fever
O = Absence of acute rheumatic fever
H = Heart disease
? = Uncertain

FIG. 3

Fig. 3 shows the complete material arranged by families. From this source the following tables have been drawn:

Table I presents the cases distributed numerically, according to sex, from combinations of affected and nonaffected parents, and the affected or nonaffected state of the offspring.

Tables II and III show the percentage distribution of affected

males and females calculated from the two sets of totals shown in Table I: Of the 234 offspring, 88, or 37.6 per cent, were affected; of the 105 males, 37, or 35.2 per cent, were affected; of the 129 females, 51, or 39.5 per cent, were affected.

Now when Tables II and III are studied certain interesting percentages appear. In each instance where the male parent is affected the percentage of affected male offspring is lowest. When the male parent is nonaffected the percentage of affected sons in rheumatic fever families is highest.

To draw conclusions from so small a series as this is unwise. But the suggestion which this distribution of affected offspring makes is that affected fathers appear to contribute a certain protection to their sons. Another possibility is that the rheumatic-fever-susceptible character is a sex-linked one.

It will be observed that more than one-half the affected boys were those whose mothers had rheumatic fever and whose fathers did not. When the father is affected it would seem that he transmits a defense to the sons which offsets this possible sex-linked susceptibility character derived from the affected mother. This defense seems to be denied to the daughters, who appear from all standpoints to possess greater susceptibility to the disease. The rate of affected daughters appears to be almost equally high from all affected parent combinations. At this point attention must be called to the case of the fourth parent combination, in which both father and mother are shown as nonaffected. We have found 2 cases at least in which the nonaffected mother of affected offspring possessed siblings who were affected (see Family No. 47, Fig. 3). This suggests the possibility that while the mother does not develop acute rheumatic fever herself, she may carry the susceptible gene.

Notwithstanding the difficulty of demonstrating the heredity of immune characters, one cannot escape in the figures reported, the very strong indication of genetic influence which determines the susceptibility of an individual to acute rheumatic fever. The heredity of special body form is, of course, well known, and our studies of acute rheumatic fever patients have shown that they possess certain typical and constantly recurring morphologic characters. This observation lends support to the belief that immune characters may also be inherited. Consequently the importance of genetic studies to the clinician is obvious and the information upon which it is based is possible to obtain with care and patience even from the dullest type of hospital patient.

Summary of Rheumatic Fever Study. 1. With 37.6 per cent of 234 offspring from rheumatic fever families affected, the factor of an hereditary susceptibility cannot be overlooked.

2. Girls are somewhat more often affected than boys.

3. Sons of affected mothers appear to derive a defense character from an affected father.

4. It is suggested that the acute rheumatic fever susceptibility character may be a sex-linked one.

General Conclusions. 1. Three examples of parakinetic effect on the psychic panel of personality are given.

2. Idiokinetic modifications are exemplified in cited cases of familial diabetes, mesodermal fault, rheumatic arthritis and rheumatic fever.

3. It may be said then that the study of constitution can be divided into two fairly well-defined fields of endeavor. First, and not without great value itself, is the direct, objective investigation of the man himself, the "up-to-the-instant" specimen, the phenotype. For this purpose classification by disease and study by the panel system have been of interest, not only as part of the general consideration of the nature of man, but also because they have proved of direct practical usefulness in diagnosis.

The second phase of constitution study leads to the consideration of the factors which produce the phenotype. These are essentially the internal and external relations, the idiokinetic or hereditary forces and the parakinetic or environment forces. The latter are, perhaps, more easily investigated. But at this time, with the mechanisms of heredity divulged by Mendel,[25] Weissman,[26] Morgan[27] and others at hand to guide us, physicians can no longer afford to neglect the clinical significance of the idiokinetic factor in human constitution.

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THE BACTERIAL FLORA OF CANCER OF THE BREAST.

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This study was undertaken because of the frequency with which micrococci were found in smears of protein precipitates from breast cancers. An added stimulus was the fact that these organisms conformed in morphology to those obtained from malignant tumors and recently described by Nuzum,[18] who was of the opinion that they played an etiologic role in the production of cancer.

The bacteria which occur in breast cancers may arise from two sources: (1) Direct invasion from the nipple region through the ducts during lactation, periods of congestion or following trauma; (2) deposition by filtration from the blood stream during periods of blood-stream invasion by microörganisms. That the second source is a rather common cause for the presence of bacteria in the organs of the body was pointed out recently by Warren and Whipple[24] (1924). They showed that under ordinary conditions organisms are continuously penetrating the intestinal mucosa and entering the circulating medium. The bacteria become filtered out and deposited in the organs, where they remain dormant or are killed and digested by the leukocytes. The lungs, liver and kidneys are involved mainly in this process, but any of the tissues of the body may be the recipients of a few bacteria at different times.

Reports concerning the search for a parasite as a cause for cancer have occupied a large portion of the literature on tumors for the last three decades. Interest in this phase of the problem has been greatest at three periods: (1) 1904 to 1907, (2) 1913 to 1916 and (3) 1922 to 1925. Greenough[8] (1904) examined breast cancer and

normal tissues, and was of the opinion that the cancer-cell inclusions, described by Plummer, Basse and others, were not parasitical in nature. Grunbaum[9] (1906) thought these "parasites" were degenerated cells or inclusions of parts of other cells in phagocytes present in the neoplasm. In 1904 Sanfelice[19] thought the granulomata formed by saccharomyces (canis, neoformans and lithogenes) or blastomyces were sarcomata, and thus the etiology of cancer was demonstrated. Braunstein[4] (1906) did not agree that these were neoplasms, as there was no metastasis or cachexia. From this time on the yeasts and their like play little part in the speculations on the etiology of cancer.

The *Lancet*,[7] in 1906, reviewed editorially the knowledge concerning the "neoformans vaccine" of Doyen which had been used in the treatment of cancer, but with little result. The organism was described as a micrococcus growing well on agar only after several transplantations and agglutinating with normal human sera in dilutions up to $\frac{1}{200}$. It had been cultivated from a "large number of tumors." Bainbridge[1] (1906) thought that patients with malignant tumors were but little benefited by the use of Doyen's vaccine, Coley's serum or any of the bacterial or serologic preparations of the time. Hansemann, Orth and Leyden,[11] in 1905, gave an excellent review of the "parasite theories," which have changed but little since this paper was published.

Karwacki[13] (1905) made cultures from 14 different tumors, including breast cancers and their metastases in lymph nodes, and obtained growths of yeasts and cocci. Descriptions of the cocci indicate that they resembled closely Doyen's micrococci and in turn resembled those cultured by Nuzum and those reported upon in this paper. Karwacki suggested that the organisms were saprophytes, having no connection with the etiology of cancer, and that they probably invaded the breast or other tumors through the skin or from the blood stream.

During the first and second decades of the last thirty years the knowledge concerning neoplasms was clarified by the better identification of lesions due to syphilis and tuberculosis and their distinction from those due to malignant disease. The next step of interest pertains to investigations centering around lymphoblastoma. In 1913 Bunting and Yates,[5,6] Billings and Rosenow[2] (1913) and others obtained diphtheroid organisms from lymph nodes of Hodgkin's disease, and the former were able to produce with these organisms an adenopathy in monkeys which they thought resembled histologically Hodgkin's disease in man. This work called forth a study of the flora of lymph nodes in many pathologic conditions. Bloomfield[3] (1913) obtained 29 strains of diphtheroids from many sorts of diseased lymph nodes, and similar findings were reported by Harris and Wade[12] (1915). Torrey[22] (1916), in 22 out of 40 cases, obtained diphtheroids as well as a few cocci from nodes involved by

widely different pathologic conditions. Sellards[22] (1916), also, found diphtheroids in 6 out of 10 spleens removed by operation. These authors all point out that there are pleomorphic types resembling micrococci present in the diphtheroid cultures. This similarity is emphasized by Mellon[16] (1917) and may be the cause for overlooking cocci in mixed cultures.

Of recent date the interest in the relation of organisms to malignant disease is manifested along three lines: (1) E. F. Smith (1922) is convinced that crown gall tumors are neoplasms because of infiltration, pseudometastases and mitotic figures in the plant cells reacting to the Bacillus tumefaciens; Levin and Levine[15] (1922) pointed out that these growths resembled granulomata. (2) Nuzum[18] (1920 and 1925), Kross[14] (1921), Mori[17] (1925) and Young[23] (1924) have cultivated organisms from breast cancers; Nuzum attributes to the micrococci which he obtained the power of causing neoplastic growth; Young was able to grow bacteria from 53 out of 59 cancers of all types; these organisms were extremely pleomorphic; many were probably diphtheroids and some cocci (occasional yeasts and the like were probably present); Mori readily obtained microörganisms from the deeper parts of 11 breast cancers and discusses the similar findings of other workers in Italy; Kross duplicated Nuzum's first work and cultured bacilli and cocci. (3) Gye and Barnard[10] (1925), have described spheroid bodies which are present in filtrable viruses and cultures of Rous sarcoma tissue; as their method is new and the field unexplored, final conclusions as to the part played by these bodies must await further investigations.

Method. The present study concerns the cultivation of the organisms occurring in 7 breast cancers and 1 specimen of chronic mastitis and polycystic disease of the breast, by the following method:

The breasts and axillary contents, still warm and wrapped in sterile towels, were received directly from the operating room. The whole block of tissue was immersed then in a 10 per cent solution of lysol for one hour. Following this the skin of the breast over the growth was seared with a red-hot knife which was used also to cut through the middle of the growth. Small blocks were cut out with sterile scissors and placed in tubes containing dextrose broth, or 0.7 per cent of sodium chloride solution. Usually six such cultures were taken from each specimen. Half of the cultures received a 2-cm. layer of sterile paraffine oil in order to produce partially anaërobic conditions for the growth of the organisms. All of the tubes were then placed in the incubator at 37° C. and examined daily until a cloud appeared around the cube of cancer tissue. At this time smears from the cultures were made and material from them was planted on agar slants and the original cultures returned to the incubator. The tubes were examined at short intervals for several weeks more.

A portion of the cancer was dissected out with a hot knife and ground up in a sterile meat grinder and cultured. A portion also was taken for histologic examination.

The work upon the first 4 cancers was done in an open room, and there were probably opportunities for contamination by air-borne organisms. At the suggestion of Dr. Hans Zinsser, a box was used which had a glass top and towel door through which the hands could be placed for the manipulations upon the other specimens studied. The box and its equipment was wet down with 10 per cent lysol for one hour before use, then the tissue was placed inside the box in a dish of the lysol. All manipulations were carried on through the towel-draped doors, with sterile instruments in covered dishes and sterile culture tubes placed in order around the dish. Thus every precaution was taken to avoid contamination by air-borne organisms during the work upon the last 3 cancers, the breast with chronic mastitis and specimens of tissue free of cancer from a breast with cancer.

None of the 7 cancers of the breast had broken down or ulcerated. There was no evidence grossly or microscopically of infection, except for occasional groups of round cells. No neutrophilic polymorphonuclear leukocytes were seen in the sections. The tumors were hard, rubbery and of the medullary type of breast carcinoma. None of the patients showed evidence of septicemia, fever or the like.

During the period of this study no normal breasts were available for cultural purposes. Autopsy specimens all had the stigmata of subpectoral instillations, septicemia or trauma and were unfit for study.

Experimental Data. Cultures were made from 41 pieces of the 7 breast cancers, 4 bits of tissue free of cancer from a breast containing cancer and 6 pieces of the noncancerous breast. The results obtained from the study of the total 51 cultures and their many subcultures made from these 8 different breasts, or 9 specimens, may be summarized as follows:

Nineteen of the cultures remined sterile even at the end of two to three months; 32 showed micrococci or diphtheroids or both. These two sorts of organisms were cultivated from each of 8 specimens and only diphtheroids were obtained from the ninth, a case of cancer. There were only 6 of the 32 positive cultures which contained no micrococci. Occasionally cultures showed the presence of a few staphylococci. There was usually no gross change in the cultures for a week or more after inoculation, but in from five to sixteen days they became cloudy and smears showed the presence of micrococci and diphtheroids. Sometimes these organisms, which always grew slowly, were detected only after subcultures had been made. The bacteria were grown in successive cultures for two to

six months, and showed many pleomorphic forms of cocci and diphtheroids. These two types of organisms were grown in pure culture and grew best in fluid media, but flourished on agar after several transplantations. The presence or absence of an oil layer over the fluid culture media seemed to make little difference in the growth of the organisms. There was no significant difference in the number or kind of cultures obtained from the specimens when the glass-box protection was used in dissecting the tissue and when it was not employed.

The diphtheroids which appeared in many different spindle, club-shaped and other forms were Gram-positive and grew on agar as dirty white, greasy, dry colonies.

Dr. Nuzum very kindly supplied to us a culture of the organism which he studied. A subculture of another sent to the Department of Pathology of the Harvard Medical School also was obtained. The organisms from both of these sources were often pleomorphic and conformed exactly to Nuzum's description. They usually formed small, flat, moist, pale, opalescent, discrete colonies on dextrose agar and plain agar slants. They were Gram-positive, small in size and tended to form short chains of 2, 4 or 6. The micrococci which were obtained from the breast specimens I studied were not only all identical in the type of colony they formed and in their morphology, but identical in these respects to Nuzum's organisms. The desirability of studying further the precise nature of these organisms is recognized.

In dilutions from 1 to 1, to 1 to 100 neither 4 normal human sera nor 4 sera from patients with cancer of the breast showed precipitations or power to cause agglutination or lysis of these organisms. The serum of one patient did not agglutinate any of the organisms obtained from the cultures of her own breast tumor or any of the others. After three subcutaneous injections into a rabbit of dead organisms grown from this patient's breast tumor, the rabbit's blood serum in dilutions up to 1 to 50 caused slight precipitation of the organisms, but it showed no cross agglutination or precipitin reaction with the patient's serum or that from other cases of breast cancer.

A killed culture of micrococci cultivated from one of the breast cancers gave no "skin reaction" in the patient from whom this tumor was removed, nor did it in another patient with cancer of the breast.

Discussion. Every one of the 7 cancers of the breast yielded some positive cultures. The regularity with which micrococci and diphtheroids could be obtained suggests either a gross contamination with only two types of organisms or the presence of these organisms in the breast tissues.

The occurrence of the micrococci in the breast with polycystic disease and mastitis and no cancer, and their presence in a portion

of breast tissue entirely free from cancer tissue, shows that the distribution of the micrococcus is not confined to the cancer tissue. Its presence does not necessarily presuppose cancer, as pointed out by Kross.[14] Diphtheroids have been obtained easily from many types of tissue, including cancer of the breast, so that neither they nor micrococci necessarily become an etiologic factor in the production of cancer. As reported in the paper following this one, experiments with the organisms I obtained from breast cancers and with Nuzum's failed to produce tumors or even warty growths on repeated injections in mice and rabbits.

The chances of contamination of the cultures during manipulation are great. A single contaminating organism could multiply in a week or so to the proportions found in the cultures studied. A pure culture of the micrococci, however, when planted in fluid medium grows exceedingly slowly. This is not influenced by an oil layer to any appreciable degree. The habit that the micrococcus has of growing at the bottom of a tube may be accounted for by the partial anaërobic conditions under which it normally grows in the breast or simply because it sinks in the fluid medium from the effect of gravity. Very likely an air-borne contaminant would fail to grow out under these conditions, because if staphylococci had been found in the cultures they became absent after two or three weeks' growth, as told by a study of smears. Furthermore, if these organisms had been present they would have appeared upon the agar slants made at the time of the first culturing. This they did only rarely and most of these first slants were sterile. Only after several subcultures in fluid medium did the micrococcus grow with ease on agar slants. Their growth was then only apparent after thirty-six to forty-eight hours. Most air-borne contaminants would grow with greater ease than these micrococci, and they were not recovered from dextrose agar plates exposed in the laboratory; some staphylococci and a few diphtheroids did appear on these plates. The absence of the common skin cocci was a distinct surprise, as it was expected that they could readily gain entrance to the breast by way of the nipple and ducts.

The nature of the bacterial flora of normal human breast tissues is interesting to speculate upon, but there is little available data concerning it. Veterinarians have collected a great deal of information about the flora of mammæ in animals, but as cancer of the breast is infrequently seen in them there is little of comparative value to be gained from such information.

History repeats itself. The micrococcus cultivated by Doyen, Karwaki and many others in 1904 to 1905 is again cultivated in 1923 to 1925 as a habitant of breast cancer.

The very presence of diphtheroids, cocci and the like, in organs free of neoplasm as well as those involved by one, speaks for their

lack of influence in the etiology of the neoplasm directly. The widespread occurrence of bacteria in the organs of the human body under apparently normal conditions is emphasized again. This should be borne in mind when attributing to any parasite the specific power of producing a neoplasm at a given site in the human body.

Summary. 1. Micrococci and diphtheroids have been cultured readily from cancer tissue obtained from 7 human breasts, without obvious areas of infection. They also were present in a breast with chronic mastitis and in parts of a breast not involved by cancer.

2. It would appear that these organisms are casual inhabitants of the breast structures, and play no direct part in the production of cancer of the breast.

3. The literature bears witness to the fact that Nuzum's micrococcus, which seems the same as the one described here, has been obtained at different times in the past though given various names.

I wish to thank Dr. George R. Minot for his constant encouragement and assistance which made this work possible.

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THE REPEATED INOCULATIONS OF ANIMALS WITH SO-CALLED "CANCER ORGANISMS."

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It is now well known that the repeated application of various chemical substances, especially tars, can lead to the production in many kinds of animals, of a variety of malignant and benign tumors. Recently Kotzareff,[3 4] by electrolyzing a tar solution upon rabbits' ears, has been able to obtain epitheliomata within sixteen days after beginning the application. Narat,[8] in 1925, produced papillomata in rats by continued applications for eight to twenty weeks of such common chemicals as potassium hydroxide and hydrochloric acid. These effects can be attributed to repeated irritation. Marsh[6] (1917) failed to produce malignant tumors in mice by many different types of trauma upon the skin. He emphasized the fact that the few spontaneous tumors which occurred in his animals had no relation to trauma.

Tumor formation by bacteria has been a subject studied by many for a long time. Three very complete reviews of the "parasite theory of cancer production," from slightly different points of view, were made by Meyer[7] in 1924, by Ewing[2] in 1919 and by Wood[13] in 1925. Little evidence has been obtained about the actual production of malignant neoplasms by bacteria. If bacteria play any role in the production of a tumor it is not necessary to consider this a specific one. Their influence might be one of irritation, such as the irritation associated with the production of neoplasms by chemical substances. E. F. Smith[12] (1922) is of the opinion that the crown gall tumor in plants produced by Bacillus tumefaciens often resembles a neoplasm. What he takes for metastases in the plant indeed may be cellular hyperplasias due to the direct extension of the infectious process. A similar picture is often noted at the periphery of a tuberculous granuloma in man.

Blumenthal[1] *et al* (1924) were able to produce tumors in both plants and rats with several different kinds of bacilli obtained by culturing various human cancers. These tumors, and probably the infectious agents within them, were found by Reichert[11] (1925) to grow in 40 per cent of the rats to which they were transplanted. Both of these investigators believed that the bacilli were not the

specific cause of the granulomatous or sarcomatous tumors, but that they carried an ultramicroscopic virus which was the specific agent.

In 1921 Nuzum[9] reported the cultivation of micrococci from human breast cancers and the Crocker Fund Animal Carcinoma No. 11, and noted in 3 mice the production of tumors by single inoculations of these organisms. Kross[5] (1921) also obtained cocci from human breast cancers, but failed to produce tumor formation by their injection into mice. More recently Nuzum[10] (1925) was able to obtain pure cultures of minute Gram-positive pleomorphic cocci from "38 out of 41 early human breast carcinomata" and "from more than 100 individual mice bearing transplantable Crocker Fund Carcinoma No. 11." By inoculations of these organisms under and into the skin of 74 mice, over a period of five to seven months, he obtained "warts, epithelial horns and spreading cutaneous ulcers with localized epithelial hyperplasia," but no "primary malignant cutaneous epitheliomata." Twelve mice of this group of 74, however, were found at necropsy to have nodules in the various organs which were thought to be granulomata or lymphocytomata. He does not state the percentage of spontaneous tumor formation in the strain of mice used.

It is our opinion, apparently in contrast to Nuzum's, that there are several reasons why it is not necessary to believe that the tumor nodules arose from the inoculation of the microörganisms; among others because no malignant neoplasms were found at the site of the inoculations.

In 50 control mice inoculated with pyogenic organisms Nuzum found no neoplastic-like lesions, the mice dying of septicemia or abscesses. He, also, was able to produce chronic mastitis in a few old-aged dogs, 2 of which developed what was evidently cancer of the breast. These 2 animals may have had spontaneous tumors which grew very rapidly in the presence of infection arising as a result of inoculations.

The experiments reported here were undertaken with two ends in view: (1) To endeavor to obtain Nuzum's results, that is, the production of "precancerous tumors" in mice with the micrococci isolated by him from cancers; Nuzum very kindly gave us a culture of the micrococci. (2) To study the effect of repeated inoculations in white mice and rabbits of the diphtheroids and micrococci which we obtained from culturing breast cancers. (See previous paper.)

Methods. The white mice utilized for these experiments were healthy active adult mice between three and four months of age and were all of the same breed and source. These animals had been used sometime previously for pneumococci inoculations. The incidence of spontaneous cancer in the strain was less than 0.5 per cent, but they were very susceptible to inoculation with mouse adenocarcinoma which grew very rapidly in them. Repeated

successive passage of such tumors in this strain of mice was accomplished easily. Thus the mice injected with bacteria were not immune to cancer inoculations, though the spontaneous development of a neoplastic growth was rare.

Two hundred and forty-one of these mice, two-thirds of which were females, were divided into two groups. One group, composed of 126 mice, was used for inoculations with Nuzum's micrococcus. The second group of 115 mice was inoculated with the organisms we had cultured from several cancers of the breast.

The bacteria were grown on agar slants or in dextrose broth and suspended in a large amount of 0.7 per cent sodium chloride solution before being injected into the animals. Dilute suspensions were found necessary because a large number of any of the organisms, especially Nuzum's coccus, enhanced markedly the mortality from sepsis. Nuzum's organism was apt to penetrate the abdominal wall so that many of the mice inoculated with this coccus died of a virulent peritonitis.

In order to facilitate inoculations the hair at the site of injection was removed with a saturated solution of sodium sulphide at monthly intervals. Inoculations of 0.2 cc. of the bacterial suspensions were made intracutaneously with a fine needle in two places. Half of each of the two groups of mice were injected just anterior to the tail in the lumbar region, which is the site of most bites. The others were injected along the breast lines, over the upper abdomen. Bacteria were injected into each mouse once a week until death or for four months, when there were only 50 left alive. These latter animals, 30 from the first group and 20 from the second, were observed for two months more, when the few then living were killed. An autopsy was performed on all of the animals at the time of death and the areas of inoculation subjected to close scrutiny. Any tissue that appeared unusual, either at the site of the inoculations or elsewhere in the body, was saved and examined microscopically.

Four rabbits, also, were injected at weekly intervals for a period of three to four months with a mixture of our diphtheroids and micrococci. These injections were made into the breasts of 2 rabbits, into the scrotum of 1 and into the ear of another.

Experimental Data. Every time that the mice were inoculated with even very dilute suspensions of any of the bacteria some half dozen or so died soon afterward from a septicemia. Ulcers and "lumps" developed at the site of the inoculations in the majority of the mice. Some of these lesions persisted for a long time and later healed or disappeared, in spite of the continued injections. The formation of inflammatory and scar tissue made intracutaneous inoculation difficult, and toward the end of the experiments subcutaneous abscesses were frequent. Often these would rupture through the scar tissue, drain dry and heal quickly. As the inoculations were continued fewer ulcers occurred in the skin alone.

Most of the 50 mice that survived the weekly injections for four months died during the next two months from old age, injury or other cause. Two weeks after the injections were stopped none of the 50 mice showed lesions at the site of the inoculations, except for a very little scarring of the skin, even when large ulcers had been present some time before. There was some overgrowth of scar tissue in the subcutaneous tissues and muscles on histologic examination of these areas, but no evidence of neoplastic proliferation. In only 1 mouse of the 241 was a tumor noted. This was a tumor of the liver and apparently spontaneous in origin. It was confined entirely to the liver and had not metastasized.

The rabbits given weekly injections of 1 cc. of a suspension of diphtheroids and micrococci developed soft, boggy infiltrations in the region of the injections. In the rabbit that received the injections in the ear, the local lesion soon crusted over, dried up and healed before the next injection, even if a large wheal were made. No further lesions of the ear appeared in this animal, even after five months except scar tissue. Injections deep into the breasts produced a permanent enlargement and induration of the breast tissues. This was never red or hot, but remained indolent and swollen. The testicular inoculations caused atrophy of the testes, scar tissue formation and an occasional small pocket of pus.

The rabbits, while receiving the injections, developed large indolent abscesses, with dense capsules in the subcutaneous tissues, elsewhere than at the injection sites. There was no tendency for these to rupture and they were never red or hot. The abscesses contained diphtheroids and occasionally staphylococci. Incision, drainage and painting with iodin caused these lesions to heal rapidly. Two rabbits in the same cage receiving repeated injections of sterile protein substances from breast cancers remained healthy.

One rabbit died with a fibrinous peritonitis, pleuritis and pericarditis after being given weekly injections in the breasts for three months. A study of smears of the exudates showed diphtheroids to be present. There was a walled-off pocket of whitish cheesy purulent material in dense fibrous tissue in the two breasts. There was no evidence of direct extension through to the body cavities. The process appeared to be very chronic in type and resembled that due to tuberculosis.

Microscopic study of the breasts of the two rabbits inoculated here showed only the evidence of chronic inflammation, and no neoplasm or tuberculosis. In localized areas of the inflammatory tissue there was an arrangement of swollen connective-tissue cells which resembled the epithelioid cells in a tubercle. The appearance of this lesion, if not carefully studied, might lead one to suspect it to be a neoplastic process, because of the mitoses and the compact grouping of the swollen connective-tissue cells. There also was

seen occasionally slight, yet definite, hyperplasia of the duct epithelium and dilatation of the alveoli which were filled with débris. These reactions could not be considered neoplastic.

Discussion. The spontaneous development of tumors may account for the occurrence of the neoplasms ascribed by Nuzum to the micrococci injected into the animals he used. In his mice the metastasizing tumors did not originate at the site of the inoculations with micrococci. If his mice were of some particularly susceptible sort the repetition of trauma and scarification from the inoculations might account for the production of warts, epithelial hyperplasia and the like. This would be comparable to the production of similar overgrowths by chemical substances. Spontaneous tumors in our strain of mice were very rare; this character perhaps might make them less susceptible than Nuzum's to such lesions as he noted at the site of his inoculations.

Our failure to obtain neoplasms after repeated inoculations which caused chronic ulcerations of the skin, in the light of Narat's work, may have been due to the relatively short duration (four months) of our experiments, although he produced papillomata in eight weeks. However, our experiments are comparable to Nuzum's. The inoculations were not given quite so frequently as his, because the mice could not tolerate injections of the organisms at shorter intervals than a week. In contrast to Nuzum's experience, we found his micrococcus to be decidedly pathogenic. This difference may play some part in the explanation for the disagreement in the results.

Summary and Conclusions. 1. Two hundred and forty-one mice of a strain susceptible to mouse cancer inoculations, but in which spontaneous tumors were very rare, were given at weekly intervals intracutaneous injections of either the micrococcus of Nuzum or diphtheroids and micrococci obtained from human breast cancers. The inoculations were continued until death, or for four months, at which time only 50 mice remained alive, the others having died, usually from septicemia. These 50 mice were observed for two months more, or for a total of six months.

2. Ulcerations of the skin which readily healed occurred with great regularity. None of the animals showed any evidence of a neoplastic growth except one which developed a spontaneous tumor of the liver.

3. Four rabbits receiving weekly injections of both diphtheroids and micrococci for three to five months, showed no signs of malignant disease even at the end of six months.

4. We have found no evidence that any of these organisms play a primary role in the etiology of cancer, though an indirect role is possible.

We wish to express our great indebtedness to Dr. George R. Minot, whose kindly criticism and constant encouragement made this work possible.

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CANCER AND THE SPINAL CORD.

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The effect of cancer occurring in various parts of the body upon the spinal cord throws some light upon the general problem of cancer. There are two large groups of cases reported in the literature. In the first, metastases to the meninges, roots, vertebræ or cord itself produce changes both local and distant in the spinal cord. In the second, spinal cord changes are said to be produced by toxins originating in cancerous tumors remote from the spinal cord and entering it from the growth by lymphatic, vascular or perineural channels.

This examination of 16 cases was undertaken with the idea of investigating the latter group. The results have warranted our efforts, since we believe that it can be shown that this second group does not exist, and that all cord degenerations found in spinal cords of individuals dying of cancer are either due to a direct effect upon nervous tissue of the growth or its metastases, or to causes other than cancer.

Review of Literature. The literature is not very extensive. In 1897, Lubarsch[1] reported 18 cases, which we shall analyze presently, and concluded in favor of the existence of both groups above noted. Oppenheim,[2] in 1891, had already expressed the opinion that cancer may produce changes in the spinal cord by toxemia. Spiller and

Weisenburg,[3] Nonne[4] and others also discussed this idea. On the other hand, the publications of Marchand,[5] Peabody,[6] Heyde and Curschmann,[7] Saenger[8] and others oppose this conclusion. They showed, furthermore, that even in apparently normal cords small metastases could be found. Sicard, Forestier and Lermoyez[9] and Siebert[10] have shown the frequency of spinal metastases with spinal cord lesions in cancer of the breast.

Since only Lubarsch published negative cases, that is, cases of cancer showing no change in the cord, it is of interest to analyze his cases for comparison with our own. It is this negative group which helps materially in arriving at a correct conclusion.

These cases raise the following points: (1) Eight of the 18 cases show nothing abnormal (Nos. V, VII, IX, XII, XIV, XV, XVI, XVIII); (2) Case XI had pernicious anemia as well as cancer; (3) Cases IV and XVII had severe arteriosclerosis which could as well produce the changes noted; (4) Case X had tuberculosis and anemia, also sufficient causes for the changes found; (5) Case XIII (eighty-one years old) showed only corpora amylacea and slight glial overgrowth in the posterior columns (frequent at this age); (6) the origin of the myelitis in Case II is not clear and Lubarsch does not believe it related to the cancer. But three cases remain to prove the theory of a cancer toxemia, Cases I, III and VIII. In III and VIII extensive metastases had occurred, but no note is made about their presence or absence in the meninges or vertebræ. Case I cannot be rejected with certainty, although the meningeal changes and arteriosclerosis throw doubt upon its value as proof of the toxemia theory.

Of the 6 autopsied cases of Spiller and Weisenburg,[3] 4 were proven to have metastases in the vertebræ. The cord in spite of this was normal. The other two showed a compression myelitis, due to metastases.

Nonne's case[4] and one of Wallenberg's[11] must be rejected on account of vertebral metastases with compression. Wallenberg's second case was one of cancer of the pylorus in a patient aged sixty-eight years with posterior and lateral column degeneration extending from C-1 to S-1. The histologic description (extensive "Lückenfelder") points to a combined sclerosis.

Analysis of Our Own Cases. The anatomic and histologic findings of our cases are reported in detail. Table I shows the site of the cancer and the number of cases in each group.

A different grouping is according to findings (Table II).

Case I. Pathologic No. 3388. Female, aged thirty-five years.

Anatomic Diagnosis. Scar of radical operation for cancer of breast (right). Recurrence of cancer in old scar with metastases to liver, brain, pancreas, mesenteric lymphglands, and spleen(?). Encapsulated calcified pulmonary tubercle. Old tuberculous bronchial lymphglands. Anemia. Small atrophic kidney. Intramural fibroma of uterus. Cardiac dilatation right. Terminal pulmonary edema, slight.

Histologic Findings. Normal spinal cord.

CASE II. Pathologic No. 3414. Female, aged fifty-four years.
Anatomic Diagnosis. Recurrent cancer of breast with metastases to left femur, skin and spinal dura with symmetrical induration at region of vertebra C-VII. Anemia and emaciation. Partial atrophy and cloudy swelling of parenchymatous organs. Brown atrophy of heart and liver. Acute colitis and proctitis. Early bronchial pneumonia. Submucous and subserous hemorrhages.

Histologic Findings. Degeneration of both columns of Burdach, beginning at the fourth dorsal segment and continuing up to the medulla. Disappearance of numerous myelin sheaths and swelling of the rest; increase of connective tissue in this region. Goll's columns, Schultz's tracts and the lateral posterior root columns are intact. Normal cord below D-4.

CASE III. Pathologic No. 3423. Female, aged thirty-seven years.
Anatomic Diagnosis. Healed surgical incision scar of radical breast amputation; metastasis to lungs. Metastatic cancer in right occipital lobe of brain. Adenomata of adrenal. Fibroma of uterus. Healed pleural and lymphglandular tuberculosis. Anemia and emaciation. Acute splenic gray tumor. Decubitus ulcer.

Histologic Findings. This case is similar to Case II. Here too a slight just visible degeneration of Burdach's columns is beginning at the upper dorsal segments. The increase of connective tissue within the cord is not so marked as in Case II. There is thickening of the pachymeninges with metastases in the upper dorsal and cervical region, with degeneration of most of the incoming nerve fibers and connective tissue overgrowth.

CASE IV. Pathologic No. 3443. Male, aged seventy-seven years.
Anatomic Diagnosis. Adenocarcinoma of rectum. Endothelioma of dura of brain. Epithelioma of larynx. Adenoma of pancreatic duct. General arteriosclerosis of aorta, coronary, cerebral and peripheral vessels. Hypostatic congestion. Bronchopneumonia. Chronic passive congestion of spleen and kidney. Edema of brain.

Histologic Findings. Throughout the whole cord there is an extremely slight diminution of nerve fibers in the central part of Goll's columns with disappearance of single myelin sheaths and scanty increase of connective tissue as well as glia condensation. This condensation is most marked in the upper lumbar segments.

CASE V. Pathologic No. 3448. Female, aged sixty-seven years.
Anatomic Diagnosis. Cancer of liver with metastases to lung and regional lymphglands. Chronic valvular lesion. Fatty changes parenchymatous organs. General arteriosclerosis. Bronchopneumonia. Scoliosis, lumbar region. History of syphilis at forty-two, manifested as tabes dorsalis.

Histologic Findings. Cervical segments: In Goll's columns there is almost complete disappearance of the myelin sheaths, and also swelling and degeneration in posterior and anterior roots. Myelin degeneration in both marginal zones and in the one crossed pyramidal tract (left side). In these degenerated areas there is marked broadening of connective tissue septa which may be seen more or less in the rest of the section. The wall of the blood vessels is thickened, especially the intima, which shows splitting up in the arteries of the anterior fissure. Chronic meningitis.

Dorsal segments: The picture is similar to that in the cervical region, only the increase of the connective tissue in the posterior columns and the degenerated lateral pyramidal tract is more marked. Chronic meningitis.

Lumbar segments: The zone of degeneration is increasing, comprising the posterior columns. Numerous corpora amylacea in the degenerated areas. Chronic meningitis. Tabes dorsalis.

CASE VI. Pathologic No. 3466. Male, aged fifty-four years.

Anatomic Diagnosis. Cancer of head of pancreas with extension into common duct. Metastases to liver and regional lymph nodes. Marked jaundice (choroid plexus and dura of cord bile-stained). Abscess of right lung. Purulent and peribronchitis. Bronchopneumonia. Chronic diffuse nephritis. Early chronic gastritis.

Histologic Findings. Spinal cord normal.

CASE VII. Pathologic No. 3479. Male, aged fifty-eight years.

Anatomic Diagnosis. Cancer of liver with metastases to ribs, anterior surfaces of cervical vertebra, left adrenal and thyroid. Moderate general arteriosclerosis. Cardiac dilatation. Cholelithiasis. Peritoneal and pleural adhesions.

Histologic Findings. Moderate arteriosclerosis, more extended in middle thoracic region than in cervical and lumbar.

CASE VIII. Pathologic No. 3544. Male, aged seventy years.

Anatomic Diagnosis. Cancer of prostate with metastases to abdominal and thoracic periaortic lymph nodes and retroperitoneal tissue. Metastases to left supraclavicular glands, lungs and bones. Pyelonephrosis. Moderate general arteriosclerosis. Adenomata of thyroid.

Roentgen ray findings: Marked bone sclerosis in lower dorsal and lumbar vertebræ. Also involvement of bones of the back and left lower extremity.

Histologic Findings. In the posterior columns of the thoracic segments there is moderate broadening of the connective tissue septa and small blood vessels without myelin degeneration. No changes in the cervical and lumbar cord. Numerous corpora amylacea.

CASE IX. Pathologic No. 3612. Male, aged sixty-seven years.

Anatomic Diagnosis. Cancer of prostate with metastasis. Extensive decubitus. Adherent pericarditis. Fistula at first portion of duodenum and

gall bladder. Senile and fatty degeneration of parenchymatous organs. Abscess of scrotum. Terminal bronchopneumonia. Arteriosclerotic kidneys. Bone destruction in right half of body of fifth lumbar vertebra.

Histologic Findings. Beginning at the level of S-II to S-III complete degeneration of Goll's columns with only a few surviving swollen myelin sheaths. The axis cylinders in this territory have also partly disappeared; those remaining show marked swelling. Marked increase of connective tissue in Goll's columns and numerous corpora amylacea in the zones of the neighborhood.

CASE X. Pathologic No. 3663. Female, aged thirty-nine years.
Anatomic Diagnosis. Recurrent cancer of breast with extension to chest wall, pleura and lung.

Histologic Findings. Normal spinal cord.

CASE XI. Pathologic No. 3708. Male, aged sixty-eight years.
Anatomic Diagnosis. Cancer of ampulla of Vater with metastasis. Peritoneal adhesions.

Histologic Findings. Normal spinal cord, except for some postmortem autolytic foci.

CASE XII. Pathologic No. 3820. Female, aged fifty-one years.
Anatomic Diagnosis. Cancer of thyroid with metastases to lungs, liver, kidneys, peritoneum, pancreas, right adrenal, rectum, left orbital, heart and bones. Pressure atrophy of spinal cord in region of extradural metastasis at the level of third and fourth dorsal vertebræ. The cord in the region of the tumor is markedly thinned out and softened.

Histologic Findings. At the level of the third and fourth dorsal vertebræ, there is myelitis which is most marked in both lateral columns. Ascending secondary degeneration in posterior columns with moderate swelling of myelin sheaths and connective tissue increase. Degeneration decreasing and disappearing in the cervical segments. Lumbar segments normal. (Degeneration is patchy and seems to be due to an interference of the blood supply of the spinal cord.)

CASE XIII. Pathologic No. 3866. Male, aged fifty-one years.
Anatomic Diagnosis. Cancer of left lung with metastases to ribs, bronchial and axillary lymph nodes and liver. Bronchopneumonia. Secondary abscess and gangrene of left lung.

Histologic Findings. Normal spinal cord.

CASE XIV. Pathologic No. 3867. Female, aged fifty-three years.
Anatomic Diagnosis. Cancer of gall bladder with metastases to omentum, peritoneal and bronchial lymph nodes, liver, pancreas, kidneys, spleen, lungs, hepatic flexure of colon, heart and diaphragm. Bronchopneumonia. Arteriosclerosis of aorta. Erosion of cervix. Ascites.

Histologic Findings. Normal spinal cord.

CASE XV. Pathologic No. 3869. Male, aged sixty-four years.
Anatomic Diagnosis. Cancer of larynx with metastases to tongue, lymph glands of neck, epiglottis, esophagus and regional tissues of neck. Postoperative absence of larynx and upper half of trachea. Bronchopneumonia. Healing tuberculosis of lungs. Chronic vascular nephritis.

Histologic Findings. Beginning at the lower level of the lumbar cord there is degeneration of the myelin sheaths secondary to connective tissue overgrowth of arteriosclerotic origin in the posterior columns. In the rest of the spinal cord, the blood vessels are widened and their walls are much thickened and the connective tissue septa are broadened. Single corpora amylacea.

CASE XVI. Pathologic No. 3879. Female, aged thirty-seven yeas.
Anatomic Diagnosis. Carcinomatosis, involving adrenals, kidneys, pancreas, liver, gall bladder, diaphragm, peritoneum, ovaries, bladder, intestines, and mesenteric, aortic, pelvic, bronchial, mediastinal lymph glands, stomach and lungs. Brown atrophy of heart and liver. Parenchymatous degeneration of kidneys. Absence of left breast. Ulcer of stomach. Arteriosclerosis of aorta. Fatty degeneration of pancreas with atrophy of islands of Langerhans. Hyperplasia of thyroid.

Histologic Findings. In both columns of Gowers in the cervical segment there is diminution of the nerve fibers. Numerous corpora amylacea throughout the whole cord.

Statistics. In order to be able to acquire a better view of the 16 cases reported we have prepared the following statistics:

TABLE I.—DISTRIBUTION OF PRIMARY CANCERS.

Anatomical diagnosis.	Number of cases.	Per cent.
Breast	5	31
Liver	2	13
Prostate	2	13
Gall bladder	1	6
Lung	1	6
Larynx	1	6
Rectum	1	6
Pancreas	1	6
Thyroid	1	6
Ampulla of Vater	1	6

We have divided the 16 cases into three groups according to histologic findings:

Group I: Normal spinal cords without myelin sheath degeneration (56 per cent).

Group II: Degenerations of the spinal cord which could be traced back to gross anatomic lesions of cancerous origin just outside the spinal cord (25 per cent).

TABLE II.—DISTRIBUTION OF CASES IN THREE GROUPS.

Group.	No. of cases.	Percentage.	Anatomic diagnosis.	Age.	Sex.	Case numbers given in case reports.	Duration (in years) of disease from clinical evidence.
I	9	56	Cancer of Breast, 3	35, 37, 39	3 F.	I, X, XVI	2, 2, 2½
			Pancreas, 1	54	M.	VI	1
			Gall bladder 1	53	F.	XIV	1
			Ampulla of Vater, 1	68	M.	XI	8
			Lung, 1	51	M.	XIII	1½
			Liver, 1	58	M.	VII	3
			Prostate, 1	70	M.	VIII	1
II	4	25	Prostate, 1 } Metastases to vertebræ and meninges	67	M.	IX	1½
			Thyroid, 1 }	51	F.	XII	1
			Breast, 2 }	54, 37	2 F.	II, III	2½, 2
III	3	19	Liver, 1—Lues	56	F.	V	4
			Larynx, 1 } Arteriosclerosis	64	M.	XV	½
			Rectum, 1 }	77	M.	IV	6

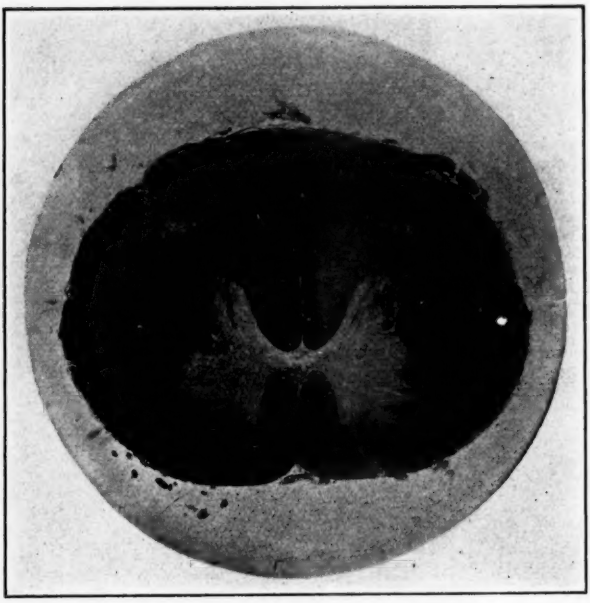

FIG. 1.—Case II. Cancer of the breast with metastases to the spinal dura. Segment C-VII. Loyez (myelin) stain. Degeneration of both columns of Burdach-Zeiss ocular 3×, objective a*.

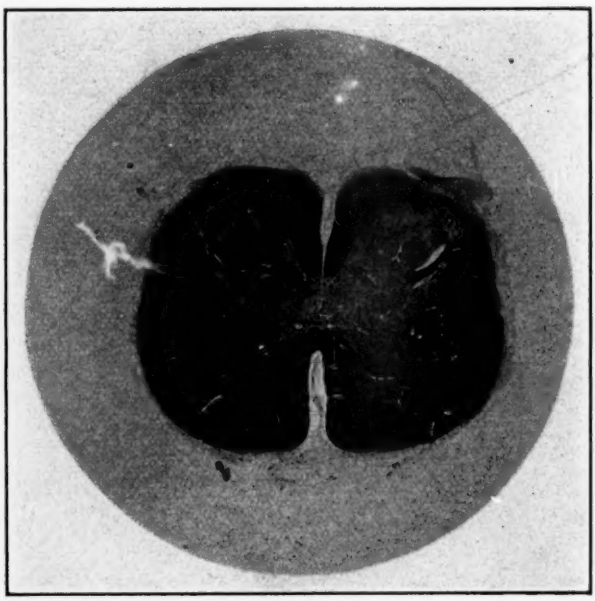

FIG. 2*a*

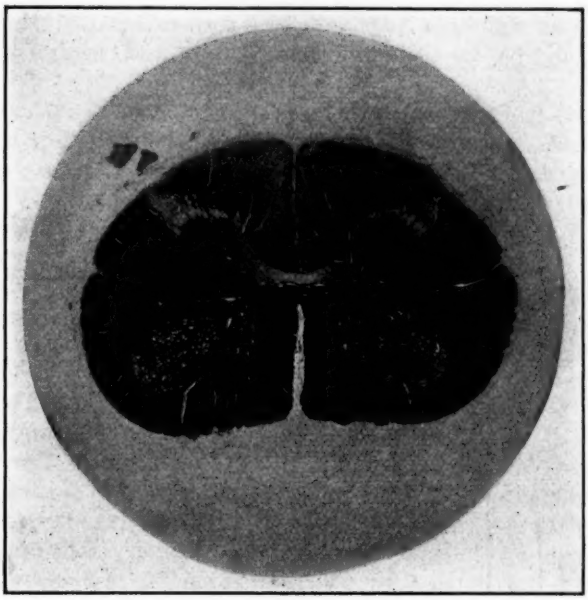

FIG. 2b.

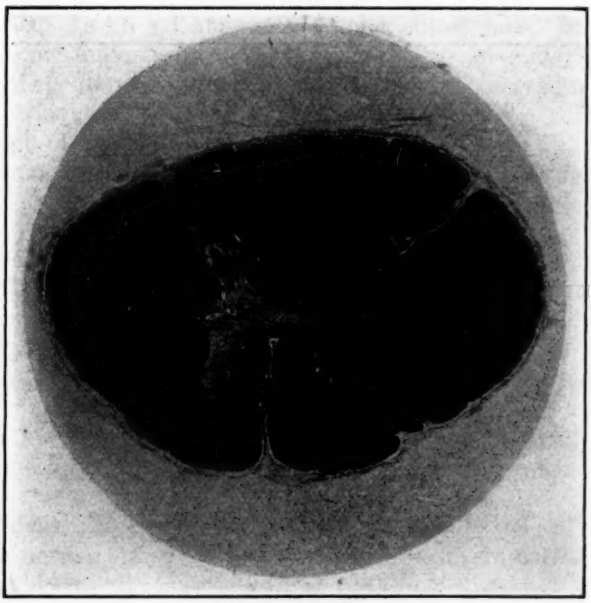

FIG. 2c.

FIG. 2a, b, c.—Case IX. Cancer of prostate with metastases to lumbar vertebræ. a, Segment sacral II. b, Segment lumbar IV. c, Segment dorsal IX. Loyez stain. Degeneration of Goll's columns. Zeiss ocular 3×, objective a*.

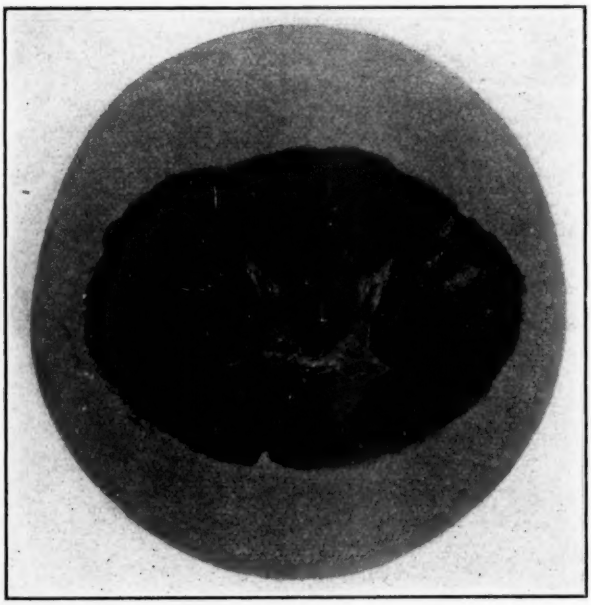

FIG. 3.—Case XII. Cancer of the thyroid with metastases to spinal dura. Segment dorsal VI. Loyez stain. Transverse myelitis with marked degeneration in lateral columns. Zeiss ocular 3×, objective a*.

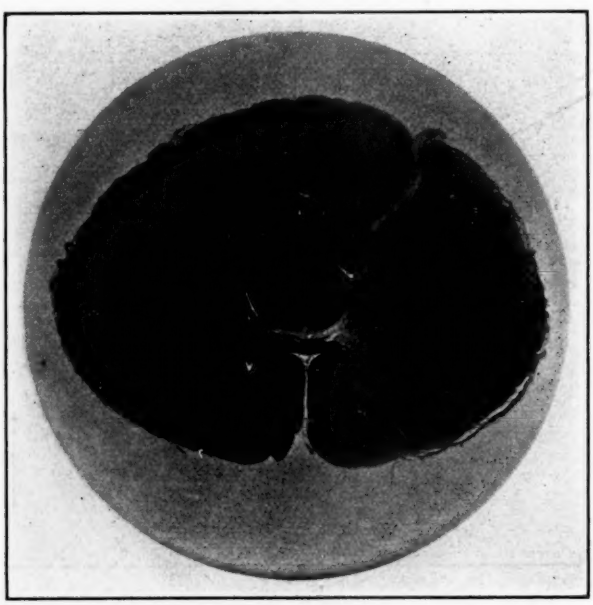

FIG. 4.—Case III. Cancer of the breast with metastases to the spinal dura. Segment cervical VI. Loyez stain. Beginning degeneration of both columns of Burdach. Zeiss ocular 3×, objective a*.

Group III: Degenerations without any evidence of causative cancerous lesions, but due to arteriosclerosis or syphilis (19 per cent).

Group I. In 56 per cent (9) of the cases the spinal cords were normal in spite of very severe cancerous disease elsewhere in the body. We wish to recall that 44 per cent of Lubarsch's cases were normal. The long duration of the disease in our 56 per cent group (one to eight years) was sufficient to produce toxic cord change, if it can occur.

Group II. In three cases (II, IX and XII) the spinal lesions are obviously secondary to metastases which produced root compression. Case II: Metastasis to the spinal dura at the level of segments C VIII–D II (Fig. 1). Case IX: Bone destruction in right half of body of fifth lumbar vertebra (Fig. 2, *a*, *b*, *c*). Case XII: Metastases to dura at third and fourth dorsal vertebræ (Fig. 3). In Case III no gross anatomical lesions were reported, which could account for the microscopic changes (Fig. 4). There is a far advanced degeneration of most of the nerve fibers of the posterior roots with increase of the intraneural connective tissue at the level of the upper dorsal and lower cervical segments together with cancerous metastases to the meninges. Therefore, we may conclude that the degeneration of Burdach's columns had an extramedullary origin and was due to metastases as in Cases II, IX and XII.

Group III. In Case V there was a concomitant lues. In Case IV the anatomic findings do not reveal any extramedullary lesions. The age of the patient (seventy-seven years) and the general arteriosclerosis adequately explain the microscopic findings. The same can be said of Case XV.

Relation of the Location of the Cancer to the Level of the Spinal Cord Changes. It is interesting that in the cases due to metastases, the changes in the spinal cord occurred at the level which seems to correspond to that of the initial growth. In the thyroid case the cord changes began in the posterior columns at D–IV, in the breast cases at about the same level, and in the prostate case at S–III. Below these levels no cord lesion was found.

We may assume that cancer cells are transported through lymph channels from the primary tumor to the vertebræ and the spinal dura at the level of the cancerous organ. Fischer[12] and recently Hassin and Singer[13] have shown such lymphatic drainage of cancer cells in metastases of the brain.

Conclusions. 1. Out of 16 cases of carcinomatosis, 9 (56 per cent) showed a normal spinal cord in the histologic examination, despite severe cachexia and long duration of the disease.

2. In cases with degenerative changes of the spinal cord, the degenerations were either secondary to dural metastases lying outside the spinal cord (4, or 25 per cent), or were caused by syphilis or general arteriosclerosis (3, or 19 per cent).

3. It could not be proven that there is a specific cancer toxin

circulating in the blood or lymph channels which acts destructively on the myelin sheaths of the nerve fibers of the spinal cord. On the contrary, our findings have shown that the spinal cord is more resistant to the influence of carcinomatosis, than the other organs of the body.

4. The metastases and the resultant cord changes are at the same segmental level as the initial cancerous growth. This has been shown by the absence of cord lesions at lower levels and by tracing upward the lesion found at the level corresponding to that of the original growth. This type of ascending degeneration in the posterior column is a frequent complication of cancer metastases to the dura and due to posterior root involvement.

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RELATION OF ABDOMINAL AND RECTAL INFECTIONS TO THE PATHOGENESIS OF DIABETES MELLITUS.*

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Recently the belief has become generally established that the underlying cause of diabetes is a pancreatitis. Many writers have noted that acute infectious diseases and hematogenous infections

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from distant foci play an important role in the causation of this pancreatitis. In this paper, therefore, I will discuss only the less understood relationship of infections of the abdominal viscera to pancreatitis and diabetes.

At the outset, we face the question: What are the paths by which infections in the other abdominal viscera may reach the pancreas?

1. Infection may reach the pancreas from other organs by direct extension by contiguity. This is possible, but it seems to me improbable. Low-grade, chronic infections seldom spread to contiguous organs unless there is a lymphatic connection between them.

2. Some writers assume that infections may spread through the lumen of the bile and pancreatic ducts. Unless there is obstruction at the ampulla of Vater (which is rare), it seems hard to believe that regurgitation of bile into the pancreas ever takes place. Urologists are coming to believe that ascending infections follow the lymphatics of the ureter, and have discarded the theory of extension of the infection through the urinary stream.

3. Infection of abdominal viscera may reach the pancreas by spreading through the general blood stream in the same way as infections from the teeth, tonsils and sinuses. This undoubtedly occurs and is of some importance in the etiology of pancreatitis.

4. Infections of the organs supplied by the portal vein may reach the liver via the portal circulation, there causing a hepatitis. Inflammation of the liver may then extend by the lymphatics to the gall bladder, bile ducts and pancreas.

5. Infection may reach the pancreas from the other abdominal viscera by way of the lymphatics. This route is emphasized by several writers and seems to me to be the most important.

Lymphatics of Pancreas. Deaver[1] summarized the lymphatic supply of the pancreas as follows: "The pancreas has a peculiarly rich lymphatic system, its vessels anastomosing freely with those of the duodenum and neighboring structures. The pancreas has no single hilum, so that the lymphatics, like the bloodvessels, emerge at various points along the surface of the pancreas and run to the regional glands, to neighboring trunks and plexuses. The regional glands are the pancreatico-splenic, superior pancreatic, superior gastric, hepatic, pancreatico-duodenal, anterior and posterior, mesenteric, mesocolic, inferior pancreatic and periaortic group of glands. To all these the pancreas sends lymphatic branches which may anastomose in the cellular retroperitoneal tissues with lymphatics from the stomach, duodenum, spleen, liver, gall bladder, bile ducts, colon and even the left suprarenal body. There is free anastomosis between the lymphatics of the duodenum, gall bladder and bile ducts with the pancreas."

Experimental Evidence. Graham and Peterman[2] found that Prussian blue injected into the wall of the gall bladder followed the lymphatics into the liver in the interlobar sheaths and also passed

down the lymphatics of the common duct and into the pancreas. An infection of the liver may, therefore, spread to the gall bladder, and, conversely, an infection of the gall bladder may spread to the liver and also to the pancreas. Graham and Peterman[2] also demonstrated that injection of pathogenic organisms into the portal vein cause a hepatitis, and the infection spreads from the liver to the gall bladder, bile ducts and pancreas. They conclude that colitis and appendicitis may lead to a secondary hepatitis, cholecystitis and pancreatitis. It seems to me practically certain that gastric and duodenal ulcer, prostatitis, and infected hemorrhoids may also lead to a pancreatitis via the portal vein or directly through the lymphatics.

Clinical Evidence. The clinical importance of the relationship of infections of the gall bladder to diabetes has been recognized by several writers. Eustis[3] has records of 36 cases of alimentary glycosuria. Of these 41 per cent have shown definite gall bladder disease during long observation and 16.6 per cent have definite symptoms of diabetes. He gives 5 case reports of patients who had gall bladder disease and glycosuria. Treatment of the cholecystitis relieved the glycosuria in all but 1 case. Maes discussed this paper and brought out the fact that the experimental observations of Archibald, Judd and Deaver have all demonstrated the intimate connections of the lymphatics of the gall bladder, bile ducts and pancreas, and expressed his opinion that infection reaches the pancreas through the lymphatics. He thinks that less stress should be laid on anatomical relations.

Harris[4] reported 2 cases of diabetes following traumatism to the pancreas, and 2 cases of diabetes resulting from pancreatitis secondary to cholecystitis. He lays stress on extension of the infection from neighboring organs, especially the colon, by contiguity, and from more remote organs through the blood stream, and barely mentions the lymphatics. One of his conclusions is: "Infections of the pancreas are usually secondary to lesions of the other abdominal viscera, though other foci of infection, as the teeth and tonsils, may be the primary cause." In discussing this paper, F. M. Allen expressed his belief that the significant lesion of diabetes is a pancreatitis, and emphasized the advisability of the "surgical removal of infectious foci, whether in the gall bladder, appendix, tonsils or anywhere else" for either the prophylaxis or the treatment of diabetes.

This problem has been attacked from the biometric standpoint by Rabinowitch,[5] analyzing the statistics of the Montreal General Hospital. He concluded that nine times as many patients had both cholecystitis and diabetes as would be expected if the influencing factors were completely independent. The incidence of diabetes was greater with cholecystitis than with cholelithiasis. He also expressed the opinion that "If hyperglycemia is accepted as evidence

of pancreatic insufficiency, after excluding the other usual causes, the incidence of pancreatitis is much greater than is generally regarded in cases of cholecystitis and cholelithiasis."

The following 5 cases of diabetes all had severe infections of the abdominal viscera at the time of the development of diabetes, or in the recent past. Their case histories are given below.

Case Histories. CASE I.—Mr. K., business man, aged forty-nine years, first consulted me in November, 1923. His mother had had diabetes for about fifteen years prior to her death from nephritis at sixty-nine years of age. His family history was otherwise negative. His personal history was important in only two respects. First, he had had symptoms probably due to a duodenal ulcer at intervals for twenty years. It was diagnosed definitely as such by Dr. Gill Richards of Salt Lake City, Utah, who confirmed the diagnosis by radiograms and fluoroscopy. Medical treatment was successful in relieving the symptoms and it has caused him no trouble for the last three years. The other point of interest in his personal history is that he has had several attacks in the last fifteen years of weakness and polyuria lasting a few days. He never had his urine examined at these times, but did have a urinalysis in 1922, which was normal. When I saw him first in November, 1923, he was recovering from a mild acute respiratory infection. There was extreme polydipsia, polyphagia, polyuria, weakness and prostration. There was marked weakness and ataxia in both lower extremities and a characteristic steppage gait. Physical examination was otherwise negative except for chronically diseased tonsils. His teeth had been removed on account of pyorrhea six years previous. His blood pressure was 135 (systolic) and 85 (diastolic). Urinalysis showed 8 per cent sugar and large quantities of the acetone bodies. The blood sugar was 350 mg. per 100 cc. Dietary measures, following Joslin's test diets, were not successful in improving the clinical or urinary symptoms, so insulin (Lilly) was given with pronounced success. Its effect on the ataxia was especially marked, complete recovery of this symptom resulting about ten days after commencing insulin. Soon after the patient became sugar free, it was necessary to begin reducing the dose of insulin, which had reached 15 units three times daily. In January, 1924, he had his tonsils removed under procain anesthesia. A week later insulin was entirely discontinued, and he did very well for about six months without it. January 5, 1924, his blood sugar was 170, and a month later it was 140. In August, 1924, his blood sugar had again risen to 240, and he had been losing weight in an attempt to keep his urine sugar free. Insulin was again recommenced and he is now taking about 30 units a day and doing very well with a blood sugar of 150.

My interpretation of this case is that infection entered the pancreas continuously for many years from the duodenal ulcer, and that there were several acute infections of the pancreas. His blood sugar had doubtless gradually risen for some months, and the febrile attack in which I saw him, precipitated a so-called acute diabetes which would probably have terminated fatally if insulin had not been available. Some recovery of the pancreatic infection followed, but sclerosis and fibrosis continued until now he probably has very little normal pancreatic tissue remaining.

CASE II.—Mrs. B., housewife, aged forty-one years, came to me June 10, 1924, complaining of weakness, loss of weight, and severe epigastric pain. She said she had had difficulty with her stomach for about fifteen years, and she had tried many diets with little relief. She had eaten very little for several days, and I was surprised to find a heavy trace of sugar in her urine. Upon examination, I found that her blood sugar was 90 mg.

per 100 cc.; that her teeth were in good condition; her tonsils had been removed; there was marked tenderness over her gall bladder and slight tenderness over her appendix. Her perineum was badly relaxed and the uterus was somewhat prolapsed. Exploratory operation under ether demonstrated a chronically diseased gall bladder and appendix and cholecystectomy and appendectomy were performed. Her pancreas was enlarged and hard on palpation. There were no symptoms of postoperative acidosis, and convalescence was uneventful save for marked glycosuria. Dietary control following the Joslin method produced a sugar-free urine within two weeks after the operation, and her carbohydrate tolerance increased so that within six weeks she was on a fairly liberal diet. She found, however, that she could not eat foods containing sugar without glycosuria. She has had two or three exacerbations in which more strict dietary control was necessary, but on the whole she has felt very well since her operation.

The comparatively low blood sugar in this case was probably due to marked undernutrition the week before the withdrawal of blood. An unsuccessful attempt to secure blood at the time of the postoperative glycosuria was made, failure being due to extremely difficult veins. This case probably represents the transition between alimentary glycosuria and true diabetes mellitus. Removal of the source of infection has probably arrested the progress of the diabetes.

CASE III.—Mr. J., farmer, aged sixty-two years, weighing 198 pounds, came to me on March 15, 1924, suffering with shortness of breath, polyuria and polyphagia, and weakness. His family history was negative for diabetes. He had had several negative urinalyses during the last forty years, the last one being in April, 1922, when he was operated upon for acute appendicitis. As the appendix ruptured during the operation, his convalescence was very stormy, and drainage continued for about eight weeks. He had had several attacks of subacute appendicitis during the preceding three years. After leaving the hospital, his health was apparently good except for a postoperative hernia. In June, 1923, he returned to the surgeon who had done the appendectomy for repair of the hernia. A routine examination of the urine at that time showed a large quantity of sugar. He was dieted until sugar free and then operated on under local anesthesia and made a good recovery. He did not continue to diet, and in March, 1924, the urine showed 4.5 per cent sugar and large quantities of the acetone bodies. Physical examination was entirely negative. He was placed on the Joslin test diets, and became sugar free in about a week. His shortness of breath and acetonuria cleared up rapidly. Strict dietary control resulted in a loss of about 25 pounds of weight, and he felt much better than since his appendectomy. He still shows sugar when he digresses even slightly from his rather strict diet, but feels well and is no longer losing weight.

My interpretation of this case is that infection of the pancreas occurred prior to and following the appendectomy. The long period of drainage certainly made conditions ideal for the spread of infection both via the portal vein to the liver, and directly via the lymphatics to the pancreas.

CASE IV.—Mrs. H. B., aged sixty years, was admitted to the Spa[1] with a rectal abscess, rectal fistula, hemorrhoids, severe hypertension and diabetes mellitus. She had had an operation for hemorrhoids twelve years previously and rectal infections of greater or less severity since. Sugar was first found in her urine about a year before her operation for hemorrhoids,

[1] I am greatly indebted to Drs. W. E. Nicely and C. C. Edmondson of the "Spa" of Waukesha, Wis., for permission to report Cases IV and V. At my request Dr. Edmondson reviewed his files and furnished me the notes on these cases. He informs me that they have had many patients suffering with cholelithiasis or cholecystitis and with diabetes at the same time.

but was controlled quite well with dietary treatment. There were, however, occasional exacerbations. Examination upon admission revealed a blood pressure of 180 (systolic) and 96 (diastolic), internal hemorrhoids, and rectal abscess, and blood sugar of 0.275 per cent and urine sugar of 0.63 per cent. Treatment consisted of dietary control and insulin, but no improvement was noted until a week after admission, when the patient was sent to a rectal specialist and the abscess drained. Thereafter the blood sugar decreased satisfactorily, and a larger diet was possible with the same insulin dosage and better control of the disease resulted. The blood pressure also declined to 156 (systolic) and 66 (diastolic).

In this patient the rectal infection and the diabetes seem to run parallel and a causal relation between the hemorrhoids, and rectal fistula, and the pancreatitis seems evident. That an exacerbation of the diabetes should result from an abscess anywhere is to be expected, but in this case response to surgery was more marked than usual.

CASE V.—Mrs. A. K. G., aged fifty-two years, was admitted to the Spa November 8, 1921, with a history of a rectal fistula of at least ten years' duration. The symptoms had become worse nine months before and there had been pain and a purulent bloody anal discharge and loss of weight ever since. In October, 1921, her rectal fistula was operated upon, and shortly after the operation she began to notice thirst, frequent urination and some weakness. Sugar was found in the urine at that time. Upon admission to the Spa her urine showed 0.35 per cent sugar which disappeared after the second day upon a diet of 1325 calories, carbohydrate 37, protein 72, fat 99. After she had been sugar free for three days her blood sugar was 0.14. There was considerable diacetic acid on admission and it slowly decreased and disappeared in fifteen days. Her carbohydrate tolerance increased rapidly under treatment and she was discharged with a diet of 2000 calories, with a little more than 100 grams of carbohydrate daily. The blood sugar remained normal for two and a half years, but in the last one and a half years (tested every four to eight weeks) has remained below 0.15 per cent.

The history of a mild rectal infection for at least ten years and a severe rectal infection for six months preceding the onset of diabetes suggests a causal relation between the two conditions. The fact that the diabetes was first recognized only after the radical cure of the fistula would seem to show that the severe rectal infection which preceded the operation had caused an exacerbation of a chronic pancreatitis. This pancreatic infection subsided quite rapidly under treatment and no recurrence has been noted of either the diabetes or the rectal fistula. The relatively high blood sugar at present indicates that the pancreas was definitely crippled by the preceding infection and future exacerbations are likely.

Comment. These cases and those previously reported in the literature indicate that abdominal infections often precede and accompany the development of diabetes. Furthermore, surgeons have long recognized that inflammatory processes in the pancreas accompany cholecystitis. Doubtless many cases of temporary glycosuria occur which recover spontaneously with the subsidence of the causative pancreatitis. On the other hand, progressive diabetes may result from cicatricial and degenerative changes long after the subsidence of the acute pancreatitis, in the same way that valvular or myocardial disease may not become apparent until long after the causal inflammatory process has subsided.

The undoubted relationship which exists between overeating,

obesity, and diabetes has been emphasized by Joslin[6] and many other writers. It would seem that overeating or obesity alone is an insufficient etiologic factor, since exercise of a healthy organ usually causes hypertrophy rather than atrophy or disease. May it not be that overeating and obesity predispose to constipation, colitis, cholecystitis and hepatitis, and that these in turn cause a pancreatitis. When the pancreas becomes infected from these or any other sources, overwork by an excessive ingestion of carbohydrates tends to aggravate this infection and clinical diabetes results.

Summary. 1. The underlying pathologic change in diabetes in many cases is a pancreatitis.

2. This pancreatitis may originate in acute infectious diseases, and from hematogenous focal infections.

3. Five cases of diabetes mellitus apparently secondary to abdominal and rectal infections are reported, with improvement following surgical intervention.

4. The opinion is ventured that in these cases the infection reached the pancreas through the lymphatics, either directly or by way of the portal circulation.

5. The conclusion is suggested that abdominal and rectal infections are important etiological factors in the etiology of diabetes mellitus.

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RESPIRATORY QUOTIENT CURVES IN DIAGNOSIS OF DIABETES.

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The glucose tolerance test—blood dextrose curve and urinary-dextrose excretion—is generally accepted as the deciding factor

in the diagnosis of a doubtful case of diabetes. However, many different methods of interpretation of this test have been used; so that, from the same experimental data, opposite diagnostic conclusions may be drawn by different observers. A great deal of this difference of opinion is attributable to lack of uniformity of technique—the amount and form of dextrose administered, the time of taking samples, previous diet or fasting, and so forth. There is, however, practical unanimity in the general idea that two factors in the blood-dextrose curve should be considered in making a diagnosis: (1) The maximum height to which the blood sugar rises; (2) the time required for the blood sugar to return to normal. Some observers claim more value for one of these factors than for the other, and a few claim either one or the other to be the only factor of diagnostic import.

John[1] states that "sufficient practical information may be secured by a test of the fasting blood sugar and a second test made three hours after the patient has received 100 gm. of glucose by mouth. The blood-sugar level in the second test will determine whether or not the patient is a diabetic—if it is high he is a diabetic, if it is normal or below normal, he is a nondiabetic."

We have encountered many cases in which the blood dextrose dropped to normal within three hours after the administration of dextrose and in which there existed undoubted abnormality of sugar-handling capacity, shown by a rise, during the three hours, of the blood dextrose to more than 180 mg. per 100 cc.

On account of the disagreement in the diagnosis in such cases and on account of our clinical impressions of the presence of diabetes, it seemed necessary to look beyond the simple glucose-tolerance test for some more definite and final information concerning impaired sugar-handling capacity.

Attention was naturally drawn toward respiratory quotient studies. When carbohydrate alone is burned within the body the respiratory quotient rises from the normal 0.82 or 0.85 toward 1 or even slightly above. When fat alone is burned the respiratory quotient falls to 0.70 or even lower. In diabetes the respiratory quotient, after a fast of twelve to fourteen hours, varies between 0.65 and 0.80 depending upon the severity—the more severe, the lower the quotient.

However, the fasting respiratory quotient alone is of little value in diagnosing a doubtful case of mild diabetes since the variation from normal is but slight. On the other hand, the fasting respiratory quotient, considered as the first point in a curve of semi-hourly respiratory quotients following heavy dextrose ingestion, is absolute evidence of the normality or abnormality of the sugar burning mechanism. We have made such studies simultaneously with the conventional glucose-tolerance tests in a series of 20 cases—normals, diabetics, and renal glycosurics. In this preliminary

report we present a typical example of each group together with the details of technique, so that others may add to the experimental data, which, in certain cases, directly contradict the conventional interpretation of the dextrose tolerance test. If the blood dextrose rises above 180 mg. per 100 cc. during the test the patient is diabetic regardless of a quick return to normal.

If: (1) The now generally accepted definition of diabetes mellitus—more than temporarily impaired sugar-burning capacity—be accepted; (2) if, in a given case, definite impairment of sugar-burning capacity be demonstrated by abnormally low fasting respiratory quotient and abnormally small rise in respiratory quotient after a dextrose meal—then we consider that diabetes mellitus exists, whether the blood-dextrose curve be conventionally diabetic or nondiabetic.

The technique followed was similar to that used by Finley and Rabinowitch,[2] by Ladd and Richardson,[3] and by Paullin[4] in their studies of renal glycosuria, and by Sanger and Hun[5] in their study of hyperthyroidism.

The subjects, for the most part, were patients who had been in the hospital from two to ten days on strictly controlled diets for the purpose of treatment for, or diagnosis of, suspected diabetes. The diets previous to the study were, therefore, in most cases, restricted in carbohydrate portion.

The night before the test the patient was given his usual light supper at 5.30 to 6 P.M. and was put to bed not later than 9 P.M. The usual basal metabolic rate preparation was followed, in that all exercise, excitement, food and temperature changes were eliminated. The subject was given no breakfast. At 7.30 A.M. a blood sample for dextrose determination was taken and urine was voided, measured and tested quantitatively for dextrose. Between 7.30 and 7.45 the patient was transported from room or ward to the metabolic station on a comfortable wheel stretcher without muscular effort on his part and allowed to remain motionless until 8.15, when a ten-minute period of expiratory air was collected in the spirometer. At 8.45, after an interval of absolute rest, this respiratory test was repeated as a duplicate or check of the former one. At 9.00, coffee-flavored or lemon-flavored glucose, 1.75 gm. per kilogram of body weight, was given by mouth. At 9.30, blood and urine samples were taken for dextrose determinations. Urinary output was measured. At 9.45, respiratory exchange was measured. Blood and urine samples were taken again at 10.00, 11.00 and 12.00, and respiratory exchange was measured at 10.15, 10.45, 11.15 and 11.45.

The urinary sugar was determined by the method of Sumner[6] and the blood sugar by the method of Folin and Wu.[7] The respiratory quotients were determined by the customary Tissot spirometer, Haldane gas analysis method. The Collins chain-compensated

spirometer was employed. The gas analysis apparatus of Harris[8] with rapid absorption bubbling oxygen pipette and electric heater was used. The gas samples were collected in Bailey[9] sampling tubes. The general gas analytic technique of Boothby and Sandiford[10] was followed. Basal metabolic rate was calculated upon the Harris and Benedict[11] standards.

By this method there were studied simultaneously the effects of heavy glucose ingestion upon: (1) Urinary dextrose output; (2) blood dextrose level; (3) respiratory quotient; (4) total ventilation rate; (5) metabolic rate. The changes in the respiratory quotient gave most definite information concerning the sugar-burning capacity. In the series of normal cases the respiratory quotient rose quickly from the normal fasting average of 0.82 to 0.85 to 0.96, 0.98 or 1 and fell back toward normal within the three-hour test period. In a case of hyperthyroidism the respiratory quotient rose above 1. In the cases of renal glycosuria the respiratory quotient curves were indistinguishable from the normal, confirming the work of Finley and Rabinowitch,[2] Ladd and Richardson[3] and Paullin.[4] In the series of diabetics, however, the fasting respiratory quotients varied between 0.65 and 0.80 and, after the dextrose ingestion, rose slowly and little. The more severe the case, the slower and the less was this rise. These findings are in accord with the conclusions of Richardson.[12]

The following results are typically normal: Case IX, Wtt.: Blood sugar, 80, 141, 124, 112, 60; respiratory quotient, 0.82, 0.81, 0.89, 0.96, 0.94.

The following results are typical of a mild diabetic: Case I, Cx.: Blood sugar, 108, 174, 225, 215, 60; respiratory quotient, 0.82, 0.83, 0.83, 0.86, 0.78, 0.80, 0.80.

The following results are typical of a severe diabetic: Case XIV, Kll.: Blood sugar, 270, 320, 400, 488, 472; respiratory quotient, 0.73, 0.72, 0.73, 0.71, 0.70, 0.77, 0.73.

Case XIV was referred as a mild or border-line diabetic with a fasting blood sugar of but slightly above normal. Without repeating the blood-dextrose determination the patient was given the routine test as outlined. The heavy dextrose meal was administered before the 270 mg. fasting blood-sugar report was received. Subsequent clinical developments in this and several other cases convince us that severe diabetics are more or less permanently harmed by administration of large quantities of dextrose, so that the study of a large series of such cases is not justifiable.

Summary. Respiratory quotient studies, before and every half hour for three hours after the administration by mouth of 1.75 gm. of dextrose per kilogram body weight, are a direct index of the normality or abnormality of the sugar-burning mechanism.

By such respiratory quotient curves absolute differentiation may

be made between diabetes mellitus and renal glycosuria, and diabetes mellitus may be diagnosed earlier than by the usual glucose tolerance test.

A number of cases, whose blood sugar rose above 180 mg. per 100 cc. blood and returned to normal in less than three hours, were shown by respiratory quotient curves, to be definitely diabetic.

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THE EARLY DIAGNOSIS OF PREGNANCY BY METHODS OF PRECISION: FURTHER OBSERVATIONS ON SUGAR TOLERANCE TESTS. FINAL REPORT.

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In our preliminary report,[1] the literature was reviewed, different techniques were cited and finally, a series of 39 cases was presented using our own modification of the technique of Frank and Nothmann with a 95 per cent accuracy in the diagnosis of early pregnancy. Since that time the use of laboratory procedures for the early diagnosis of pregnancy has increased so enormously, that now we feel a survey of these methods, their possibilities and shortcomings, to be warranted. It must be remembered throughout this discussion that no laboratory method has yet been devised which is absolutely and infallibly diagnostic of the presence or absence of pregnancy (except Roentgen ray in the late months), and therefore the indication for the use of these tests is to strengthen the already present suspicion of pregnancy, or the probability of its absence. The

experimental work in this field has been dominated by two ideas. The first is based on the supposition that pregnancy causes a specific protein, possibly in the nature of a ferment, to appear in the maternal blood; the second, on the observation that pregnant women in the early months are prone to glycosuria, which is usually transient, harmless, and can easily be induced by the feeding of carbohydrate. Our attention will focus mainly about the latter group, for it is now fairly well proven that there is no protein specific to the pregnant female, at least so far as these tests can show.

The first group embraces the following:

I. *The Abderhalden Reaction.* This is based on the supposition that reaction will occur between the ferments in maternal blood serum when brought in contact with an extract of fresh placenta, using ninhydrin as the indicator. Its present status is best described in the conclusions of Smith and Shipley, "While the natural ferments present in serum are somewhat increased, there is no evidence that a specific ferment exists in pregnancy" and "the large number of positive results on the serums of men and nonpregnant women proves the test of no value for the diagnosis of pregnancy." Added to this, the actual technique of the test is so complex as to require an unusual degree of serologic skill in its performance.

II. *Erede's Anaphylactic Reaction.* This author proposes the theory that the "fetal proteins" in maternal blood should cause an anaphylactic reaction in smooth muscle, when perfused through the uterus of a sensitized virgin guinea-pig. No experimental work could be found to substantiate this thought.

III. *Costa's Novocain-Formalin Reaction.* To 1.5 cc. of 2 per cent novocain in citrated saline solution, add 3 drops of the blood to be tested, centrifuge, and add 1 drop of pure formalin. A gray precipitate appearing within fifteen minutes is considered diagnostic of pregnancy. The reports on several series of cases show that normal blood will react positively within three to fifteen minutes, and the test is also positive in infections and toxic conditions. It must therefore be discarded as allowing too large a factor of error.

IV. *Dienst's Reaction.* To 10 cc. of distilled water add 2 drops of the serum to be tested. Place 2.5 cc. of this mixture in a test tube, and add 1.25 cc. of a 33 per cent sodium hydroxid solution. The tube is shaken and 20 drops of copper sulphate solution added. A blue supernatant ring is supposed to be diagnostic of pregnancy. The most striking results come from Milan, Italy, where 130 women in the early months of pregnancy did not even show a convincing majority of positive reactions. No favorable report of this test has been found by us in the literature.

V. *Red Blood Corpuscle Sedimentation Test.* Into a syringe containing 0.2 cc. of 5 per cent sodium citrate solution, 0.8 cc. of the patient's blood is drawn. The mixture is then discharged into a specially calibrated upright tube. The length of time necessary

for the cells to pack below the 18 mm. mark is the observed standard. In the normal this is supposed to be one hundred and twenty minutes, and in the early months of pregnancy a much shorter time should be noted. This phenomenon has found its greatest use as a prognostic aid in gynecologic infections, and in pulmonary tuberculosis, but has proved entirely worthless in the diagnosis of early pregnancy, for which it was originally conceived by Fahraeus.

The reactions in the second group are:

I. *The Alimentary Glycosuria Test of Frank and Nothmann.* In pregnant women, after feeding 100 gm. of glucose on a fasting stomach, glycosuria without hyperglycemia will appear within the course of two hours. This fact is only noted with any constancy during the first three months of pregnancy, and immediately disappears following the separation of the placenta from the uterine wall, or upon the death of the fetus. This is the laboratory method to which we wish to call attention, and in a later paragraph will devote further discussion to it.

II. *The Roubitschek Adrenalin Test.* Feeling that the above procedure was too involved, this investigator fed his subjects only 10 gm. of glucose on a fasting stomach, and at the same time injected 0.5 mg. of adrenalin hypodermatically. The appearance of glycosuria within two hours was considered by him diagnostic of pregnancy. It soon became apparent in a larger series of cases, and from the reports of other workers, that no trust could be placed in this test, for the results were bizarre and inconstant. It has therefore been practically abandoned.

III. *The Phlorizin Test.* Phlorizin is a glucosid derived from the bark of the domestic apple tree, and is a favorite drug for inducing a lowered kidney sugar-threshold in laboratory animals. Since glycosuria without hyperglycemia had been noted constantly in pregnant women, Kamnitzer and Joseph reasoned that a phlorizin glycosuria should be relatively more easily induced in these patients than in the normal nonpregnant woman. That is to say, a threshold already low could be more easily lowered to the spilling point than could a normal one, and should necessitate a smaller dose of phlorizin to accomplish this purpose. They found this optimal dosage to be 2 mg. of the drug. After ascertaining that a preliminary urine specimen is free from sugar, they inject 2 mg. of phlorizin hypodermatically, the patient having fasted for twelve hours. If, within the next two hours, sugar appears in the urine, the presumption of pregnancy is strong. This test also loses any significance after the third month.

The simplicity of this technique, and its ease of administration, have appealed to the majority of workers in this field during the last two years, especially since the appearance of a proprietary preparation, "Maturin," which is a solution of 2 mg. of phlorizin and beta-eucain, in ampoules. In our preliminary report we tabulated

the results of work on this test, and showed that too many nonpregnant control cases reacted positively. The following table will add more convincing proof of this fact and will bear out the conclusion we then arrived at: "The phlorizin technique has yielded no satisfactory results." We had intended to continue our phlorizin series, but abandoned the idea in view of the number of reported failures with this test.

TABLE I.—RESULTS OF INVESTIGATORS USING THE PHLORIZIN TECHNIQUE.

Observer.	No. cases.	Pregnant. Positive. (per cent.).	Pregnant. Negative. (per cent.).	Nonpregnant. Negative. (per cent.).	Nonpregnant. Positive. (per cent.).	Men, Positive. (per cent.).
Kamnitzer and Joseph	300	98	2	90	10	*
Craincianu and Goldenberg	50	100	0	46	54	*
Klaften	300	80	20	*	*	*
Perez and Brea	116	85	15	95	5	*
Bronicoff	300 (1000 tests)	74	26	96	4	72
Bodo	175	86	14	84	16	*
Eastman	136	90	10	92	8	*
Ewald	150	78	22	97	3	*
Krauter	149	74	26	80	20	*
Tomay	?	91	9	73	27	*
Marbatto	?	100	0	75	25	*
Rychlinsky and Gottlieb	?	39	61	64	36	*

* No tests performed.

Discussion of Alimentary Glycosuria Test. Convinced by our preliminary work that we were dealing with a fairly accurate procedure for aiding the early diagnosis of pregnancy, it became our aim to so simplify the actual technique of the test that it might be used in the routine of any general practitioner. The original technique of Frank and Nothmann was so cumbersome as to prohibit its use anywhere except in a hospital. Our present practice is as follows:

1. Patient shall take an average supper the night previous.
2. Collect first morning specimen of urine. This must be negative for sugar by Fehling's qualitative test, before the glycosuria test is begun.
3. Omit breakfast.
4. The calculated dose of table sugar is given, dissolved in two tumblers of water, flavored with half a lemon each. The dose is computed by using 7.5 gm. of table sugar for every 10 pounds of body weight, except that the maximum total must not exceed 150 gm. It has been our experience that Franklin granulated table sugar is best for this purpose.
5. Voluntarily voided specimens of urine are collected one hour and two hours after the dose is taken, and in cases going to operation

the same day, or under any nervous strain, a third hour specimen is also collected. These are tested for sugar by the Fehling's qualitative method.

6. We have largely dispensed with the collection of blood for sugar determination, but when necessary, have found that it should be done one and a half hours after the test is started. Our records show that the blood sugars of 33 pregnant women averaged 0.138; and of 19 nonpregnant averaged 0.125 during the test. If either of the hourly specimens of urine shows a definite reduction of the Fehling's solution such as would be termed "positive for sugar" in a routine urinalysis, the test is considered positive, and in conjunction with the clinical findings, strengthens the probability of pregnancy. The opposite is true for a negative test.

Certain pitfalls have been encountered in the course of these experiments which are worthy of mention. Several patients have not considered the "lemonade" appetizing enough and have relegated the second glassful to a convenient sink, or out the window. Others have become truly nauseated by the dose, and have vomited, making the test untrustworthy. In this connection it is well to note that false positives will almost inevitably result in patients who are intolerant of sugar in any form, as evidenced by a history of nausea on eating any sweet foods or candy, a fact noted by the patient before there is any suspicion of pregnancy. Patients with endocrine obesity, exophthalmic goiter, diabetes, or any severe hepatic disturbance, are not amenable to this test, because their carbohydrate metabolism is already abnormal.

It will be noted that a third hour specimen is counselled in certain cases. This is because we have seen patients vomit a large amount of the sugar solution as late as three hours after the test was completed, while being anesthetized for operation. This occurrence is probably due to pylorospasm, and an extra specimen will reduce the factor of error in such cases. Routine blood sugar determinations were not made in this series, because the early work had shown that this type of glycosuria is accompanied by normal glycemic values. In only one case so far has this proved to be untrue. The patient was diagnosed pregnant with the aid of the test, and this was later confirmed, but during the observations her blood sugar rose to 228 mg. per 100 cc. of blood.

If the suspicion of another pregnancy arises during the lactation period, this reaction may be used as a diagnostic test, providing that all urines showing reducing substances shall be subjected to a yeast fermentation test for twenty-four hours to determine that glucose and not lactose is being excreted. Failure to take this precaution may lead to a false positive result, as in the following case: A lactating woman complained of gastric disturbances leading her to suspect another pregnancy, and her uterus was found slightly enlarged. After the sugar test, her urine was reported "positive

for sugar." At a subsequent examination the uterus was no larger than previously and at operation she was found to have multiple fibromyomata of the uterus. A recheck showed that no fermentation test had been done on the urine, which vitiated the value of the result.

It is important that credence be given only to those reactions in which there is either a frank reduction, or no reduction, of the Fehling's solution. The middle ground, reported by the laboratory as "trace of sugar" or "slight reduction of Fehling's," is very treacherous, and caused annoying error until the above criteria were established. Seven of our patients undergoing the test were reported to have a "trace" of sugar, most frequently in the specimen of the second hour. Of these cases, 3 were not pregnant, 2 were four and five weeks pregnant respectively, and 2 were one and three days postpartum respectively. Under these circumstances the test must either be repeated or discounted entirely.

Exclusive of the cases already cited, and a group of "dead ovum" cases to be detailed below, we wish to report a carefully followed-up series of 150 cases, of whom 88 were pregnant and 62 were not pregnant. Of the pregnant group, 83 women (94 per cent) reacted positively, and 5 (6 per cent) reacted negatively. In the nonpregnant group, 57 women (92 per cent) reacted negatively, and 5 (8 per cent) reacted positively. A truly specific test for pregnancy should not yield any positive results in nonpregnant women, and the failures in this series occurred in the following cases:

Two cases of pelvic inflammatory disease.

One patient whose period was overdue, but who menstruated normally ten days after a positive test.

One patient with the symptoms and gynecologic findings of an early ectopic pregnancy, and leukocytosis of 14,400. Abdominal section revealed absolutely normal pelvic genitalia.

One patient, thought to be pregnant, who proved to have a fibromyoma of the uterus.

Two women were successfully diagnosed pregnant at the third week after conception by means of this reaction. Our former conclusion that the test is of no value after the third month was also confirmed in this series.

Aside from its use in the early diagnosis of pregnancy, another phase of this reaction has proved of great value to us. It was stated by the original investigators, and corroborated in our work, that the death of the fetus, or the separation of the placenta from its implantation site will cause the reaction to become negative. The importance of this fact when applied to threatened abortions, or incomplete miscarriages with retention of a large residuum, is immediately obvious, especially to those who practise prompt evacuation of a dead ovum. In a series of 9 such cases ranging from the ninth week to the third month of pregnancy, a negative reaction

confirmed the suspicion of a dead ovum and enabled us to immediately evacuate the contents of the uterus. Thus, when a negative test supports the clinical history, we feel it is an invaluable indication for operative interference in cases of dead ovum, and suspected inevitable miscarriage. It has never caused us to make a mistake, and the economy it effects in days of hospital waiting is evident.

A recount of all the interesting patients met in this series is impossible in the allotted space, but certain outstanding ones may be appropriately cited. On August 1, 1925, a young unmarried woman presented herself with the history of coitus three weeks previously and amenorrhea for three days beyond her menstrual time. A test done at this time showed a "trace of sugar," and she was told to return in a week for further trial, when a definite positive was obtained. She was seen again on August 21st, and in the interval had suffered three days bleeding due to ergot, and had indulged in coitus once. The test was still positive. She reported again on September 8th, and showed the breast and gynecologic signs of early pregnancy, and the test was still positive. The patient induced an abortion a few days later. This is a most unfortunate aspect of the reaction in that it affords unscrupulous characters too much certainty at an early date in pregnancy. Here too it may be noted that unless there is a missed period between the suspected coitus and the date of the test, a negative result will be obtained, even in patients who later prove to be pregnant. This observation may help to substantiate the theory that the ovum of the first missed period matures into the fetus, as is already surmised from the fact that women who menstruate irregularly always pass beyond the calculated gestation time.

An interesting instance of this reaction after the third month was seen in Mrs. D., who in the fifth month after her last seen period fell over a chair, and was brought to the hospital. From the clinical picture it was evident that a miscarriage was inevitable, and as a routine we ran the glycosuria test, which was definitely positive. The explanation for this seeming paradox appeared with the fetus, for its heart was still beating after birth.

A patient aged forty years, came to the hospital complaining of three months' amenorrhea. She had the history and physical evidences of a hemiplegia four years before, and in addition, examination revealed an arteriosclerotic hypertension, and a fairly firm uterus enlarged to the size of a three months' pregnancy. In view of a positive sugar test, the diagnosis of early pregnancy, rather than early menopause with myoma, was made and an operation advised. A three months old fetus was removed by abdominal hysterotomy.

Summary. 1. The methods of precision for the early diagnosis of pregnancy are reviewed, and the alimentary glycosuria test shown to be the one in which most trust can be put.

2. An extremely simple technique for the performance of this test is offered, using table sugar, a lemon, and Fehling's solution as apparatus. The technical pitfalls of the test are outlined.

3. A new series of 150 cases is reported with 6 per cent error in the early diagnosis of pregnancy, and 8 per cent error in nonpregnant women. Although this percentage of error is larger than we experienced in our preliminary work, it still is smaller than that found with any other laboratory method for the early diagnosis of pregnancy, and compares favorably with such procedures as the Wassermann test in its factor of error. We therefore believe this test is useful, and if practised routinely, will aid appreciably in the diagnosis of pregnancy before the gynecologic signs appear.

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PASSIVE ANAPHYLAXIS IN A HEMOPHILIAC.

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Instances of passive anaphylaxis in the human subject are not common, and we, therefore, thought it would be of some interest to report a case of it occurring in a hemophiliac boy. We have been unable to find any references in the literature to its occurrence in man, although it has repeatedly been brought on in animals.

We have reported elsewhere[1] the changes induced in hemophiliac blood by the induction of a local skin reaction. Sheep serum is usually used for sensitization, unless the patients are already sensitive to horse serum. If not already sensitive, they are given 3 to 4 cc. of sheep serum subcutaneously, and ten days later 0.22 cc. intradermally. The clotting time falls promptly to normal as the reaction comes on, and the blood itself is rendered almost normal in all its clotting elements. If bleeding is in progress, it stops completely. These effects persist for periods varying from one week to several months and the reaction may be repeated as often as needed. It is our custom to have the hemophiliac patients report every few weeks to have their clotting time tested. If found prolonged, they are given an intradermal injection of the protein solution to which they are sensitive. The skin reaction does not desensitize the individual, so that he is constantly ready to respond at any time that he is injured, or bleeding arises from any cause. It was this type of treatment we were attempting to use in the instance cited below when we obtained the passive anaphylactic reaction.

Case Report. D. H., K8852, white, aged nineteen years, was admitted to the Cincinnati General Hospital, November 20, 1925, bleeding from his gums and from the sockets of three molar teeth extracted the day previously. He gave a history of frequent and protracted bleeding following minor injuries throughout his childhood. His maternal uncle was a "bleeder." His blood was examined on admission and was found to be typical of hemophilia, that is, with a deficient thrombin forming mechanism, as recorded and discussed in another paper.[1]

Desiring to try the method of Vines[2] in correcting the patient's hemophiliac tendency, we gave him an intradermal injection of 0.2 cc. of normal horse serum to test for sensitivity. The reaction being negative, he received 4 cc. of the same serum subcutaneously

to bring on sensitization. In the succeeding week, while awaiting the development of sensitization, it was necessary to give two whole blood transfusions of 400 cc. each from two of his brothers (not bleeders). Neither of these transfusions stopped the bleeding. On the eighth day following the subcutaneous serum injection (November 20, 1926), he was again tested for sensitization by the intradermal injection of 0.2 cc. of serum. Not the slightest trace of reaction developed, much to our surprise. About five and a half hours later he was given 800 cc. of citrated blood from his brother-in-law, who was known to be sensitive to horse serum. The bleeding was not altered during, nor immediately after, the transfusion. Usually, if a transfusion is to be effective in arresting bleeding, its effect is in evidence while the blood is being given. About thirty minutes after the completion of the transfusion, it was noticed that a typical protein reaction was developing at the site of the intradermal serum injection six hours previously. The bleeding ceased as this reaction developed, nor did it again recur. The reaction subsided in a few hours, and reappeared several times in the next six days, being less severe and of briefer duration as time passed.

This appeared to be an instance of anaphylaxis in which the individual acted as a passive receptacle for the reacting agents. The patient was clearly demonstrated to lack sensitization to horse serum by the intradermal injection several hours before the transfusion. When given the blood from the sensitized donor, the reaction took place at the site of the earlier skin injection, and nowhere else. There were no systemic disturbances attributable to a general reaction. The tissues of the boy contained the serum injected, and presumably when the antibodies of the transfused blood reached this area, the reaction developed.

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EXPERIMENTAL STUDIES ON THE REACTING POWER OF ASTHENIC PERSONS, WITH SPECIAL REFERENCE TO THEIR ANTIBODY PRODUCTION.

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As opposed to the many fields of medical sciences which possess a large experimental literature, we find but few treatments of the

question of constitutional deviations.* Although the functional aspect of this problem—inaugurated by Rosenbach and Kraus—has gained some ground, the doctrine of constitutional alterations remains notwithstanding—as Borchardt justly remarks—almost exclusively one of structure. It is desirable, therefore, to enlarge the experimental side of this question; and especially must the altered reacting power of the tissues against various irritants be carefully investigated.

In pathophysiologic experiments we sometimes observe atypical reactions which cannot be interpreted in any other way than by the altered reacting power of the organism. It is just in this field that problems must be analyzed, according to the suggestion of Martius, with particular care, and attention to the possible occurrence of some constitutional factors.

The asthenic constitution has always been regarded as a type with diminished reacting power. Stiller, who first described this type, emphasized in his fundamental work the torpid behavior of this asthenic organism. We find, however, only a small amount of experimental work on this interesting question. Some years ago Ullmann was able to demonstrate a weakened function of the liver of asthenic persons by means of the levulose test. We found in our experiments with strychnin, administered intravenously to asthenic persons, that their blood pressure was less influenced than that of normal individuals. A similar observation had been made by Schiff and Bálint on asthenic children, after the injection of adrenalin.

In previous investigations of the effect of typhoid vaccine, in bringing about a marked rise in the number of eosinophilic leukocytes, we were able to state that, contrasting with the behavior or normal controls, asthenic individuals reacted with no or with a very slight eosinophilia. This eosinophilia which was evoked by repeated injections of the vaccine was very similar to that observed as anaphylactic phenomena. Therefore our experiments are of great interest because they seem to be an experimental confirmation of the old observation that asthenic persons are less inclined to anaphylactic phenomena than others. In further experiments we investigated the agglutinin production of asthenic persons, inquiring whether it was possible to find differences in their antibody-producing power from those of normal persons. At this point we purposely evade the question, whether the agglutinin production could be taken as a measure of antibody production, as various authors have done who were studying the effects of the socalled protoplasm activators.

In the description of the properties of the asthenic type of individual we often find mentioned empirically that persons having this

* The reader is referred to Dr. George Draper's recent book on the Human Constitution.—Ed.

structure are often attacked by various infections, especially tuberculosis. This striking disposition of asthenics was interpreted as due to diminished defensive power of the asthenic organism, caused probably by a failure in antibody production—a supposition which, although apparently corroborated by many experiences, was, however, scarcely demonstrated by experimental investigations. Reviewing the literature of this subject, we were able to find only one paper, by A. Meyer, who stated that asthenic persons show a strikingly lessened fat-antibody production against tuberculosis, as a sign of their weakened defensive powers. Here is another field of experimental pathology that is very much neglected, as is demonstrated by the fact that in the books of such authors, as for instance J. Bauer, Borchardt and Hart, we seldom find such studies mentioned.

Experimental work on this problem is connected with many difficulties in prosecution and a multitude of possible errors in interpretation. Thus at first it must be recollected that the production of antibodies is a wavering one. We know, for instance, that overstrain, cold (Friedberger, Trommsdorf), use of alcohol (Friedberger), and many other factors may have a very great influence on the antibody level of the blood. Nutrition also plays an important part. Müller found in his experiments on pigeons that when nourished with milk and bread they showed twice as much antibody formation as the pigeons receiving only potatoes as food. The influence of age, sex and state of development must also be considered. Thus it would seem that only the results of carefully controlled experiments, always made under the same conditions, can be considered as yielding conclusions of value.

Bearing in mind all the considerations mentioned above, we have made experiments on thirty-four asthenic persons, investigating their agglutinin production after injections of typhoid vaccine. All of our cases were well marked and pure forms of the asthenic type and the results obtained were compared with those obtained from many controls kept under exactly the same conditions. The method was mainly that adopted by us in previous investigations.[1,2,3] Asthenics and controls were injected at the same time with a polyvalent typhoid vaccine (Besredka); all receiving 3 injections within fourteen days. The persons submitted to this treatment were mainly young persons, who never have had any severe disease (typhoid or similar disease!), never had been vaccinated and had never received any active therapeutic treatment whatsoever. Many of them were admitted to the clinic and thus we were able to make our investigations under the same external circumstances. The examinations for the agglutinin values were made with a twenty-four-hour agar culture of an agglutinable strain of typhoid bacillus. The end titers of the sera of the vaccinated persons were obtained every third or fourth day in a period of three weeks.

The effect of the vaccine treatment was mostly very marked. The agglutinin level in the blood of the vaccinated control persons, rose generally to 1 to 2000, 1 to 3000 and often as high as 1 to 6000. Also the patients suffering from slight diseases (slight apical processes, neurasthenia and so forth) showed mostly similar values, as given in the following table:

TABLE I.—MAXIMUM AGGLUTININ TITER IN NONASTHENICS.

Case No.	Sex.	Name.	Age.	Diagnosis.	Agglutinin titer.
1	M.	Sz. S.	38	Diabetes mellitus; slight acidosis	1 to 1800
2	M.	M. J.	31	Duodenal ulcer	1 to 2600
11	F.	Sz. J.	22	Gastroptosis	1 to 2200
19	M.	Sz. J.	24	Neurasthenia	1 to 3200
25	M.	B. J.	26	Neurasthenia	1 to 3400

The agglutinin titers reached by our asthenic persons (Table II) show a striking difference.

TABLE II.—MAXIMUM AGGLUTININ TITER IN ASTHENICS.

Case No.	Sex.	Name.	Age.	Diagnosis.	Agglutinin titer.
1	F.	D. M.	29	Habitus asthenicus	1 to 800
5	M.	J. S.	23		1 to 50
6	M.	B. K.	17	Asthenia	1 to 150
7	F.	P. E.	23	Cat. apicis	1 to 1000
8	F.	V. F.	21	Asthenia	1 to 200
10	M.	Cs. J.	31	Asthenia ptosis ventr.	1 to 200
12	M.	M. J.	17	Asthenia ptosis ventr.	1 to 350
13	M.	Sz. K.	31	Asthenia ptosis ventr.	1 to 400
14	F.	T. Gy.	28	Asthenia ptosis ventr.	No agglutinin
17	M.	Sz. R.	20	Asthenia	1 to 450
18	M.	B. F.	16	Asthenia	1 to 2400
21	M.	T. S.	23	Asthenia	1 to 500
23	M.	K. F.	24	Asthenia	1 to 400
26	F.	B. E.	20	Asthenia	1 to 400
28	F.	J. G.	24	Asthenia	1 to 600
31	F.	G. E.	19	Asthenia	1 to 400

These cases demonstrate conclusively the great differences in the agglutinin production of normal and asthenic persons receiving injections of typhoid vaccine. In the asthenic we find striking diminished values, contrasting strongly with those of normal persons, and reaching for the most part to less than a third of the normal values. We were able only in few cases to find values approaching those of vaccinated normal persons. As to the time of onset of agglutinin production, there was no great difference between asthenics and normals. Sometimes we had the impression

that the greatest agglutinin values appeared somewhat later in the asthenic.

From these experiments a *defective antibody production of the asthenic organism must be admitted.* Whether a constitutionally weak antibody production or only the defective function of certain systems is responsible, we cannot decide. From our experiences we may, however, assume, that the increased susceptibility of asthenics to various infections, as mentioned in the introduction, may be connected with such circumstances as the weakened antibody production that our experiments demonstrate. At all events *these investigations show clearly that in the various types of constitutional deviations we are able to find not only structural, but also functional alterations which may be of great value in the somatic and functional evaluation of the owner.*

Summary. Persons having the signs of asthenic constitution showed a very diminished reacting power against various irritants.

When injected with a typhoid vaccine which had a strong eosinophilotactic effect, they reacted with no, or very slight, eosinophilia.

The agglutinin production of these persons is also much decreased. This latter fact may be very important in explaining the old observation that asthenic persons, having probably a weakened antibody production, are often attacked by various infections.

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THE VALUE OF THE ROUTINE EXAMINATION OF CEREBROSPINAL FLUID.

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The cerebrospinal fluid has been subject to more or less investigation ever since the modern method of lumbar puncture was introduced by Quincke;[20] it has become especially important in

recent years, as lumbar puncture is performed routinely in every carefully studied case of suspected central nervous system involvement. It is our purpose to endeavor to correlate the more important findings in the routine examination of the fluid with their proper clinical interpretations, and to call attention particularly to the value of the accurate determination of its sugar content.

Since an understanding of the mechanism of production and absorption of cerebrospinal fluid is essential to an intelligent interpretation of alterations in its physical and chemical composition, we shall briefly summarize the salient features of these physiologic processes, quoting largely from the work of Boyd.[1]

The fluid enters the subarachnoid system chiefly through the ventricular choroid plexuses, invaginations of pia through the choroid fissures. The exact method of production is still a matter of dispute. The choroid plexuses possess a lining of differentiated epithelium closely resembling the alveolar cells of secreting glands, and furthermore, under stimulation, as by ether, changes are observed in these cells similar to those noted in actively secreting glandular cells. However, although under conditions of abnormal stimulation the process may be one of active secretion, it is probable that normally the forces involved are those of filtration and diffusion, modified to a large extent to what Mestrezat termed "elective filtration." An additional source of supply, according to many authorities, which cannot be considered secretory in nature, is by way of the perivascular prolongations of the subarachnoid space, which are formed by the extension of the arachnoid along the cerebral arteries to their capillary terminations, where the membrane becomes incorporated with the vessel wall, the space terminating in a cul-de-sac. Communicating with these perivascular spaces are similar spaces around the nerve cells, the perineuronal spaces. Dercum[22] denies the existence of continuity, anatomic or physiologic, between the subarachnoid space and the perivascular, pericapillary and perineuronal spaces. He considers these lymphatic in nature, comparable to tissue spaces elsewhere and serving as a medium of nutrition to the central nervous system, a function which he does not ascribe to the subarachnoid space and spinal fluid.

The fluid finds its exit mainly through the arachnoid villi into the blood stream. A second means of absorption is supplied by the perineural extensions of the subarachnoid space, emptying into the tissue lymph spaces. These perineural sheaths are especially marked in the case of the olfactory, optic and auditory nerves, but are found accompanying all cranial and spinal nerves.

The total quantity of cerebrospinal fluid is approximately 120 cc., which amount is completely replaced every five to six hours. The greatest part by far is absorbed into the blood stream, the two

main factors involved being the lower pressure of the venous blood and its higher osmotic tension. Normally there exists a constant balance between production and absorption. It has been shown that an increased flow follows intravenous administration of extracts of choroid plexus and disintegrating brain tissue and also of paretic spinal fluids, normal fluids having no effect. Conditions of acidosis, anoxemia and anesthesia cause increased flow.[1]

The chemical composition of the cerebrospinal fluid is interesting in that it shows that there exists an effective barrier to the entrance of many substances from the blood stream. This barrier must be the epithelium of the choroid plexuses and perhaps the lining of the capillary terminations of the subarachnoid space. We find that comparatively few substances are able to pass from the blood into the fluid. Alcohol, chloroform and acetone gain easy entrance, and urotropin only in slight amounts. On the other hand, absorption from the fluid into the blood stream takes place with extreme facility and rapidity.[1]

That the mechanism of spinal fluid production is not one of simple filtration is further shown by its protein, nonprotein nitrogen and sugar concentrations. The protein content of blood plasma is approximately 6.8 per cent, that of cerebrospinal fluid between 0.15 and 0.40 per cent.[19] The nonprotein nitrogen values of the fluid range from 15 to 20 mg. per 100 cc., 10 to 15 mg. of which are represented by urea nitrogen, as urea, being very diffusible, exists in all body fluids in practically the same concentration. In uremic states, in which the nonprotein nitrogen content of the spinal fluid may be 200 to 250 mg. per 100 cc., the urea nitrogen figures are within a few milligrams of these values, the creatinin, uric acid and unknown nitrogen being comparatively little increased, although the concentration of these substances in the blood is tremendously raised.[19] Likewise, with regard to the sugar content, our findings and those of others[8,9] demonstrate that its concentration in the fluid is normally approximately 50 per cent of that in the blood stream. All of these facts point to the conclusion that simple filtration cannot explain the passage of materials from the blood into the cerebrospinal fluid.

The importance of such routine procedures as the cell count, globulin estimation and the Wassermann reaction is so well known and generally recognized that it is not our purpose to dwell upon these subjects except to call attention to the special value of some of the findings as observed in our series of cases.

In 1921, at the suggestion of Prof. F. X. Dercum, Dr. V. R. Syracuse, working in our laboratories, made a study of the value of the colloidal-benzoin reaction[2] as a routine measure in the examination of cerebrospinal fluid. After employing the reaction in a number of normal cases, and in a group of known cases of syphilis

of the central nervous system, each one of which showed a 4+ Wassermann reaction, the conclusion was reached that the test added nothing to the sum total of our knowledge in any case. In fact it tended rather to confuse, for constant curves could not be obtained in the same cases at intervals of a few days and precipitation in varying degrees occurred in absolutely normal fluids. Our findings and conclusions are corroborated by the work of Warnock[3] and others.

Until recently very little work was done in the way of chemical study of the fluid apart from the simple qualitative copper-reduction test and the globulin estimation. Whatever results had been obtained in an attempt at more detailed analysis were rendered untrustworthy by the primitive state of knowledge of physiologic chemical methods. As an example, considering the quantitative sugar estimation with which we are concerned, Mott,[4] in 1910, gave the normal concentration as obtained by the Fehling gravimetric method as 150 to 180 mg. per 100 cc., whereas at present, with the simple and exact technique now available, we find the true value to be about one-third of that amount.

The study of the nature of the reducing substance in the cerebrospinal fluid began in 1858, when Claude Bernard demonstrated the presence of a copper-reducing agent which he affirmed to be glucose. Since that time a number of opinions have been entertained, but weightiest evidence seems to point toward the view originally held by Bernard. Haliburton was at first of the opinion that the substance was pyrocatechol, but later abandoned this belief. Mott[4] states that there is no doubt about the presence of glucose in the cerebrospinal fluid, the reducing body rotating the plane of polarized light to the right, giving off CO_2 upon fermentation by yeast and yielding with phenylhydrazin a typical glucosazone which melts at 205° to 206° F.

In support of this view, Kasahara and Uetani[5] have recently shown that after subcutaneous injection of insulin there is a decrease in the concentration of reducing substance in the spinal fluid and that there is some parallelism between this concentration and that of glucose in the blood. In our series of cases there are 6 of diabetes mellitus in which simultaneous blood and spinal-fluid sugar determinations were made. In all but one case(Case 6) the average normal spinal fluid to blood sugar ratio of approximately 1 to 2 was maintained. The one exception, in which the spinal-fluid sugar was increased out of proportion to the increase in blood sugar, is explained by the concomitant factor of cerebrospinal lues which, in our experience, may materially raise the concentration of the spinal-fluid glucose. In one case in which hypoglycemic symptoms followed the administration of insulin (Case 5) our findings coincide with those of Kasahara and Uetani,[5] mentioned above.

TABLE I.—DIABETES MELLITUS.

	Sugar in mg. per 100 cc.	
	Blood.	Spinal fluid.
1	220	100
2	320	151
3	190	96
4	325	118
5	236	110
(after insulin)	63	34
6	363	210

From these facts, and from evidence of a similar nature secured by blood and spinal-fluid determinations in several normal cases, we were led to the conclusion that, since the fluctuations in the sugar content of the blood, normal and abnormal, are reflected in that of the spinal fluid, either all estimations of the latter should be checked by and compared with the simultaneous determination of the blood sugar or the spinal fluid should be obtained under the same dietary precautions as are ordinarily observed in collecting blood for sugar determinations. If this is impracticable, as it often is, the time of day and relation to meals should be noted and considered in the interpretation of the values found. Our findings have recently been borne out by the work of Goodwin and Shelley,[6] who both arrive at practically the same conclusions. Although the relation of spinal-fluid sugar to blood sugar has been noted by other workers,[7,8,9,10] the widely varied results obtained by different investigators in both normal and pathologic cases is attributable to their disregard of this fact.

The problem of preservation of the fluid after collection is of importance. There is a variance of opinion regarding the occurrence of glycolysis in the fluid upon standing. Mott[4] incubated six sterile specimens of cerebrospinal fluid two days without affecting their copper-reducing power, and kept other sterile specimens at room temperature for weeks without the disappearance of reduction. He states, however, that bacterial infection will decrease or abolish this property. It has for some time been recognized that sugar is absent in cases of acute suppurative meningitis, the modern opinion being that the destruction of the glucose is effected by the glycolytic action of the polymorphonuclear leukocytes. On the other hand, it is believed that the mononuclear elements present in tuberculous and luetic fluids have little if any such action.

In this connection Levinson and Tashiro[11] have done some interesting work. They have shown that, upon standing, normal and tuberculous fluids show a decrease in hydrogen-ion concentration which is due to the escape of CO_2 from the fluid; the hydrogen-ion concentration of the fluid of epidemic meningitis, on the other hand, shows a marked increase which is due to the formation of a nonvolatile acid, lactic acid, which we believe to be the result

of the destruction of the glucose which rapidly disappears from such fluids. We interpret these facts, in the light of our findings in fluids of tuberculous meningitis, as an indication of a slight degree of glycolysis with resultant lactic acid formation in this condition, but to a much more limited extent than occurs in epidemic meningitis, in which condition practically complete glycolysis takes place.

In our early work upon the spinal-fluid sugar concentration little importance was attached to the matter of preservation of the fluid, and the inconstancy and wide variability of our results were discouraging and confusing. Acting upon the suggestion of Mr. M. Trumper, we adopted the following method of procedure in all cases and found our results to be remarkably constant and entirely trustworthy. To obviate the possibility of glycolysis and to insure standard results, the fluids utilized for our sugar determinations were, within a few minutes after collection, placed in sterile tubes containing a few milligrams of sodium fluorid. With this precaution we found that specimens of every type of case studied gave, after standing for a week at room temperature, results which checked almost exactly those obtained in our original determinations.

The technique used was that recommended by Foster,[12] a modification of the Folin-Wu method of blood-sugar determination, using a standard containing 5 mg. of glucose per 100 cc.

During the process of protein precipitation preparatory to the sugar determination it was noted that the density of the precipitate obtained paralleled exactly that observed in the estimation of the globulin content by the Noguchi method. Since the protein content of the spinal fluid is very slight, and consists almost entirely of globulins, it naturally follows that any increase in globulin may be measured, for all practical purposes, by the increase in total proteins. Our observations were controlled in over 200 cases by the butyric acid method of globulin precipitation, and as a result the following procedure is now being used routinely: One cubic centimeter of spinal fluid is diluted with 7 cc. of distilled water; to this are added in turn 1 cc. of 10 per cent sodium tungstate and 1 cc. of two-thirds normal H_2SO_4, mixing thoroughly after each addition. In this dilution, the same as that used in the precipitation of proteins from blood, normal fluids yield no precipitate or, at most, a slight turbidity, while any increase in protein is readily perceived. This method has the advantage over the Noguchi method, that the readings are made immediately, the procedure is much more simple, no heating being necessary, and the test is free from the disagreeable odor attending the use of the butyric acid reagent.

Of our series of 210 cases, 67 were normal adults. In these fluids the cells were 4 or less per cubic millimeter, the globulin was not increased and the sugar concentration ranged from 40 to 66

mg. per 100 cc., the average being 57 mg. The figures given as normal by different investigators exhibit great variation. This fact, as stated above, is due to their almost universal disregard of the essential factors of preservation of the fluid and of the dietary influence upon the sugar content of the spinal fluid. Kelley[13] states that the normal values lie between 40 and 95 mg. per 100 cc.; Foster[12,21] gives the range as 44.2 to 61.4 mg.; Nawratzki[14] and also Kopetzky[15] considered 46 mg. to be an average normal figure; Mestrezat[16] and Marie[17] report 48 to 53 mg., and Hopkins[7] 60 to 75 mg., as normal levels. We believe our figures to represent the extreme limits of normal when the fluid has been properly preserved and when the necessary dietary precautions have been observed.

Apart from this group of normal adults is one including 11 cases of children from six months to ten years of age. These must all be considered normal, and yet the sugar content was distinctly higher than that of the adult group, ranging from 71 to 90 mg., the average being 79 mg. per 100 cc. The significance of this fact we cannot explain, but it seems that the normal average in children must be considered to be 25 to 30 mg. higher than that in adults.

With a knowledge of normal sugar values and an understanding of the factors underlying the production and absorption of cerebrospinal fluid, we may arrive at the theoretically possible causes of variation in the amount of sugar and later compare these deductions with the actually determined causes of increased and decreased sugar concentrations.

Let us first consider the problem of increased sugar concentration, or hyperglycorachia. This concentration is dependent upon: (1) The blood-sugar content, as we have seen; (2) the condition of the protective barrier, represented by the lining of the choroid plexuses and possibly of the capillary terminations of the cerebrospinal vessels, which are surrounded by prolongations of the subarachnoid space. The matter of changes due to variations in the sugar content of the blood we have already gone into, and have seen that without central nervous system change the ratio of spinal-fluid sugar to blood sugar remains approximately 1 to 2 within a wide range of values extending from moderate hypoglycemia to moderate hyperglycemia. We have had no experience with extremes of either condition, our blood sugars ranging from 63 to 363 mg. per 100 cc.

Turning to the subject of changes in the protective barrier mentioned above, we come to what we believe to be the main factor underlying pathologic increases in the sugar concentration of the cerebrospinal fluid. The membranes of the body, including the surfaces of all cells, act essentially as semipermeable membranes, and substances passing through them do so in accordance with the laws governing filtration and diffusion through such structures. The surfaces of cells in general are but partially permeable to

glucose, and this may be assumed to be true of the cells now under consideration, those constituting the lining of the choroid plexuses and of the cerebrospinal capillaries. Studying the phenomena of diffusion and filtration following injuries to semipermeable membranes, it is found that in practically all cases the subsequent tendency is toward an increase in permeability or a diminution in the restraining properties of the membrane involved. So we would infer that any disease causing injury to the cerebrospinal vascular system in general, and to its capillaries and the choroid plexuses in particular, will result in an increase in the sugar content of the spinal fluid. This generalization was utilized by Kraus and Pardee[18] to explain the presence of an increased sugar concentration in cases of epidemic encephalitis.

A diminished sugar content cannot, we believe, result from any change in the vascular system, since an injury here would tend rather toward an increase in permeability. So, in accounting for a decrease we naturally think of the process of glycolysis. In fact this is probably the only agency by which the sugar concentration can be lowered independently of a diminution in the sugar content of the blood, and our values will be low in only those conditions which cause, directly or indirectly, splitting of the sugar of the cerebrospinal fluid.

Of our series of 210 cases, 99 had sugar concentrations of over 66 mg. per 100 cc., which we consider to be the high limit of normal adult fluids. These cases may be classed under five headings:

1. *Normal Children* (11 *Cases*). In these values were obtained ranging from 71 to 90 mg. per 100 cc., the average being 79 mg. From this we conclude that the normal figures for children under ten years of age are 25 to 30 mg. above those of adults.

2. *Epidemic Encephalitis* (8 *Cases*). The figures in this group were 71 to 106 mg. per 100 cc., the average being 86.1. The constancy of high values in this condition, coinciding with the results obtained by Foster,[12] Kraus and Pardee,[18] Goodwin and Shelly[6] and many others, lead us to consider this factor to be of the greatest importance in the diagnosis of encephalitis.

TABLE II.—EPIDEMIC ENCEPHALITIS.

	Cells.	Globulin.	Sugar.	Wassermann.
1	14	++	78	−
2	2	++++	106	−
	1	++++	103	−
3	1	+	91	−
	12	++	83.8	−
4	71	++	71	−
5	59	++	76	−
6	970	++	87	−
7	44	+	100	−
8	6	+	81	−
	2	+	71	−

(All cells in this and following tables are predominantly mononuclears unless otherwise stated.)

3. *Lues of the Central Nervous System* (41 *Cases*). These cases had sugar concentrations of from 30 to 110 mg. per 100 cc., with an average value of 64 mg., 16 being above 66 mg., and only 2 being below 40 mg. The predominating lesion in cerebrospinal syphilis may be vascular, meningeal or parenchymatous, and it seems reasonable to conclude that the varying pathology accounts for the variation in sugar content, the latter being dependent upon the site of greatest anatomic change. Thus, if the vascular lesion predominates the sugar will be high; if the meningeal irritation is the outstanding feature the cellular increase will be marked and the sugar be but slightly altered or may even be at the lower limit of normal; for we believe that the mononuclear cells found in luetic infections, especially the large mononuclear or monocytic elements, have some power of glycolysis, enough at any rate to counteract, if they be in great numbers, any tendency toward an increase in sugar resulting from slight vascular damage; lastly, if the chief lesion be parenchymatous there may be little or no change in either sugar concentration or cell count. The following tables, consisting of the most striking examples of the above hypothesis are very illustrative.

TABLE III.—LUES OF MENINGEAL TYPE.

	Cells.	Globulin.	Sugar.	Wassermann.
1	32	++	53	++++
2	11	++	62	++++
3	80	++	55	++++
4	48	+	47.6	++++
5	52	+++	36	++++
6	80	++	50	++++
7	69	+	40	++++
8	78	+++	57	++++
9	40	+	58	++++
10	37	+	62	++++

TABLE IV.—LUES OF PARENCHYMATOUS TYPE.

	Cells.	Globulin.	Sugar.	Wassermann.
1	5	+	43	++++
2	4	++	50	++++
3	6	+	60	++++
4	1	+	58.2	++++
5	7	++	57	++++
6	6	++	62	++++
7	4	++	63	++++

TABLE V.—LUES OF VASCULAR TYPE.

	Cells.	Globulin.	Sugar.	Wassermann.
1	2	+++	110	++++
2	7	+++	83	++++
3	2	+	68	++++

TABLE VI.—LUES OF VASCULAR AND MENINGEAL TYPE.

	Cells.	Globulin.	Sugar.	Wassermann.
1	60	+++	83	++++
2	80	++++	83	++++

4. *Marked Increase in Intracranial Tension* (7 *Cases*). Five were brain tumors and 1 brain abscess, the diagnosis in each case being confirmed by operation or autopsy. One case was of unknown etiology. In all these instances the sugar concentration was high, ranging from 71 to 110 mg. per 100 cc. In the case of brain abscess the high cellular content of the second specimen was probably due to the sudden rupture of the abscess rather than to a meningitis, thus not affording sufficient time for the glycolytic action of the leukocytes.

TABLE VII.—INCREASED INTRACRANIAL PRESSURE.

	Cells.	Tumor. Globulin.	Sugar	Wassermann.	Blood sugar.
1	1	++++	83	−	
	1	++++	71	−	
2	6	+++	110	−	
	4	+++	105	−	
	3	++++	83	−	
3	−1	++++	110	−	105
4	3	++++	71	−	
	3	+++	77	−	
	5	+++	80	−	
	7	++	87	−	
	3	++++	83	−	
5	3	+	76	−	
		Abscess.			
6	19	+++	100	−	
	5120(P)	++++	71	−	
		Undetermined.			
7	64	+++	91	−	

(One of the most characteristic features of the spinal fluid in our series of brain-tumor cases is the presence of a low cell count with an enormous increase in globulin.)

5. *Functional Mental Disorders* (57 *Cases*). These were found to have uniformly high sugar values, extending from 71 to 94 mg. per 100 cc., the average being 79.3 mg.

The cases in children and in the mental disorders we cannot explain, and must merely infer that there exists a condition of increased permeability of the choroidal epithelium and perhaps the capillary endothelium. In the instances of increased intracranial tension it seems logical to believe that this factor alone is capable of facilitating the diffusion of sugar into the cerebrospinal fluid. The matter of increased sugar in cerebrospinal lues we have discussed above, stating our belief that it is dependent upon the degree of vascular participation in the pathologic process The constancy of increased sugar concentration in epidemic encephalitis is of the greatest importance, and is due to the fact that the most prominent lesion is a perivascular infiltration of mononuclear cells, which cannot but affect the permeability of the capillary endothelium by causing at least functional if not anatomic injury.

When we consider the cases presenting a decrease in sugar content we must keep in mind the fact that such a change can be explained only upon the assumption that a glycolytic agent is present. From the work of Levinson and Tashiro[11] we infer that the phenomenon of glycolysis occurs to a great degree in the acute suppurative meningitis and, to a much less extent, in tuberculous meningitis. All of our cases showing a diminished sugar concentration in the presence of a negative Wassermann reaction fall into these two classes. Of 13 cases, 6 were instances of acute suppurative meningitis and 7 were tuberculous meningitis. In the acute group the figures ranged from 0 to 37 mg.; the latter value was obtained in a case of meningococcic meningitis after a week of treatment. All cases were fatal.

TABLE VIII.—ACUTE SUPPURATIVE MENINGITIS.

	Cells, polymorphonuclears.	Globulin.	Sugar.	Wassermann.	
1	480	++++	0	−	7-2-24
	245	++++	37	−	7-9-24
2	4600	++++	25	−	
3	9100	++++	0	−	
4	6144	++++	0	−	
5	276	++++	0	−	
6	1280	+++	0	−	

The concentration in the tuberculous cases was from 18 to 36 mg. per 100 cc., the average being 26.8 mg. All were fatal, the diagnosis in each case being confirmed by post-mortem examination.

TABLE IX.—TUBERCULOUS MENINGITIS.

	Cells.	Globulin.	Sugar.	Bacilli.	Guinea-pig.
1	154	+++	24.1	Found	+
	47	+++	35	0	+
2	52	+++	32	0	+
3	5	+	34	Found	+
4	20	++	21	0	+
5	21	+	20	Found	+
	35	+	18	0	+
6	15	++	30	0	+
7	123	+++	36	0	+

From our studies we believe the estimation of the sugar concentration of the cerebrospinal fluid to be of the utmost importance, especially in the differential diagnosis of tuberculous meningitis from conditions which may clinically exactly simulate it, with special reference to certain forms of epidemic encephalitis. It is our opinion that the presence of a normal or elevated sugar content is very strong if not conclusive evidence against the diagnosis of tuberculous meningitis, as is the presence of low normal or subnormal values against the diagnosis of epidemic encephalitis.

We have recently met with 2 cases presenting the typical clin-

ical picture of encephalitis which were so diagnosed. The spinal fluid findings were characteristic of either encephalitis or tuberculous meningitis, except for the fact that no tubercle bacilli were found. Unfortunately, quantitative sugar estimations were not made. At autopsy both cases were found to be tuberculous meningitis. On the other hand, a child was recently admitted to the hospital and the diagnosis of tuberculous meningitis was made. The history and clinical findings were typical of that disease, with the sole exception of the fact that the spinal-fluid sugar concentration in all specimens was normal. Postmortem examination revealed bilateral bronchopneumonia and a cerebellar abscess.

We also consider the sugar determination, coupled with the other spinal fluid characteristics, especially the cytologic findings, to be of aid in the more exact pathologic diagnosis of the various forms of lues of the central nervous system.

It has been our observation that, as a rule, comparatively little attention is paid to the chemical characteristics of the spinal fluid, much more clinical emphasis being laid upon the bacteriologic findings and cytology. Many cases are incorrectly diagnosed brain or cord tumors; many cases of tuberculous meningitis and epidemic encephalitis are confused, and many others are improperly diagnosed merely because of failure to attach sufficient importance to the more important detailed spinal fluid findings. We believe the sugar concentration to be of great value in many cases, and strongly urge that its estimation be made a part of every routine examination of cerebrospinal fluid.

Summary. 1. The colloidal benzoin reaction was found to add nothing of value to the knowledge obtained in the routine examination of cerebrospinal fluid.

2. A study of 210 cases with special reference to the sugar concentration of the spinal fluid gave the results shown in Table X.

TABLE X.

	Sugar.	Cells.	Globulin.	Wassermann.
Normal fasting limits in adults	40 to 66	−4	0	−
Normal children to ten years	71 to 90	−4	0	−
Functional mental disorders	71 to 94	−4	0	−
Lues of central nervous system	30 to 110	1 to 80	++	++++
Epidemic encephalitis	71 to 106	1 to 970	++	−
Tuberculous meningitis	18 to 36	5 to 154	+++	−
Suppurative meningitides	0 to 37	many polys.	+++	−
Increased intracranial tension	71 to 110	1 to 6	++++	−

3. Normal variations of spinal-fluid sugar were found with variations in blood sugar, maintaining an approximate proportion of 1

to 2, from moderate hypoglycemic to moderate hyperglycemic levels. For this reason time of day and relation to meals must be considered in taking fluids unless simultaneous blood-sugar determinations are made.

4. For constant and accurate results the fluid should be properly preserved.

5. The essential cause of hyperglycorachia is increased permeability of protective barrier of choroidal epithelium and cerebrospinal capillary endothelium. Conditions causing hyperglycorachia are those that have essentially vascular pathology, especially encephalitis and certain forms of the syphilis of central nervous system.

6. Great increase in globulin and high sugar content are characteristic of increased intracranial pressure in general and particularly of brain tumor. High sugar values were also obtained in various functional mental disorders.

7. The essential cause of hypoglycorachia is glycolysis. This occurs to a large extent in acute suppurative meningitis and to slight degree in tuberculous meningitis. In these conditions alone were subnormal values consistently found.

8. The greatest value of sugar determinations lies in differential diagnosis of tuberculous meningitis, especially from epidemic encephalitis.

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CLINICAL OBSERVATIONS UPON THE CIRCULATORY APPARATUS IN PNEUMONIA.*

An Analysis of Seventy-eight Cases.

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It has been possible to examine at the Western Pennsylvania Hospital, a series of pneumonias of all types and groups. Advantage was taken of this to subject as many of these cases as possible to a cardiovascular study, and the present paper is an attempt to analyze this material.

About 100 patients were under observation, including all varieties of lobar pneumonia and bronchopneumonia, but in these reports upon the circulatory apparatus we include 78 cases. They were begun approximately in November 1924, and ended in May 1925, about six months.

Valuable studies have from time to time been made upon the heart, and the importance of cardiac failure as a cause of death in pneumonia. Although certain other diseases are popularly supposed to be cardioselective, it must be emphasized that this disease should be given an extremely important position for its damaging effect upon the heart muscle. In a large proportion of cases it is the cause of death, but it is probable, that though the immediate effect upon the myocardium is profound, the after results are not so serious as one would imagine from the damage produced during the acute period of the infection.

There is apparently some disagreement regarding the type of heart injury occurring in pneumonia most frequently. Newburgh and Porter[1] believe that the heart muscle in this infection is essentially normal, having adjusted itself to its poisoned food as a result of very gradual exposure to the toxin in the blood.

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Recently two important studies have appeared upon the circulatory apparatus in pneumonia (William Stone[2] in 1922, and Brooks and Carroll[3] in 1920). The deductions of the latter two were based upon an analysis of 5000 protocols of patients who died from pneumonia in the A. E. F., and the former from a series of 1205 lobar and bronchopneumonia patients including 259 autopsies. He believes that the most frequent cause of death is sepsis, and that the cardiac muscle failure is the most prominent factor. In 89 autopsies of lobar pneumonia heart muscle degeneration was found in 42 per cent, right ventricular degeneration in 40 per cent and left ventricular dilatation in 12 per cent. The heart muscle was normal in 57 per cent. In 112 autopsies of bronchopneumonia the heart muscle was found to be normal in 66 per cent, the muscle was degenerated in 34 per cent, there was left ventricular degeneration in 10 per cent, and right ventricular dilatation in 37 per cent. Brooks and Carroll, in the work mentioned, maintain that the most frequent cause of death is from cardiac insufficiency, and that right heart dilatation is a great factor in determining the result.

Berry[4] gives a report of 400 autopsies on lobar pneumonia as follows: Hydropercardium, 61; cardiac hypertrophy, 98; cardiac dilatation, 6; toxic myocarditis, 15; abscess of myocardium, 1; cardiac thrombosis, 1; acute endocarditis, 14; serofibrinous pericarditis, 21; purulent pericarditis, 21. In this series the pericardium was most frequently involved.

Henry Feinblatt[5] also summarizes 139 autopsies of lobar pneumonia as follows: Purulent pericarditis, 24; pericarditis with effusion, 3; fibrinous pericarditis, 1; cardiac dilatation, 12; acute endocarditis, 1; fatty degeneration of the heart, 1. Bronchopneumonia developed 41 autopsies showing, cardiac dilatation, 4; fatty degeneration of the heart, 1; purulent pericarditis, 1; fibrinous pericarditis, 1. A further study of 300 autopsies, particularly in reference to pericarditis in pneumonia, produced 72 of various stages and types.

In estimating the amount of muscle damage the autopsy is, of course, the most satisfactory and accurate method, and in this series of 78 cases there were 32 deaths, a mortality of 41 per cent. Of these 16 were examined postmortem. Clinically the great majority of cases were critically studied, and an attempt was made to carefully analyze all the circulatory objective and subjective symptoms.

It is believed that cardiac muscle damage may be assumed to exist when it is found that there is a diminution of the cardiac impulse, a disappearance of the muscle quality of the first sound and also a marked weakening of that sound. Both the second aortic and the second pulmonic sounds are also frequently impaired and diminished in intensity. Generally with the weakening of the muscle there is a definite tendency toward a lowering of the blood pressure, and a quickening of the cardiac rate. It is frequently

possible to show an enlargement or dilatation of the left or right ventricle. Besides all these local cardiac signs there are remote and secondary findings, fine moist rales at both bases (pulmonary edema) passive congestion of other organs and cyanosis. Also as an aid to the knowledge of the functioning of the heart, electrocardiographic tracings are extremely helpful. We know moreover that it is in the recognition of myocardial damage that clinically the internist is somewhat deficient, nevertheless in this series of lobar and bronchopneumonias we have attempted to determine myocardial damage, and also to check these findings by electrocardiographic tracings on 31 patients.

The electrocardiogram, therefore, is of the utmost value in this field of myocardial clinical study. The signs which are most useful for this purpose are: (1) *P-R* interval; (2) bundle branch block and other types of intraventricular block; (3) abnormal inversion of the *T* deflection; (4) ventricular change in muscle mass; (5) auricular fibrillation and flutter; (6) marked notching and thickening of *R*. In these 31 patients many had tracings taken several times. Inspection of Table I will show the results as follows: Right ventricular preponderance, 1; left ventricular preponderance 6; abnormal inversion of *T* deflection, 5; negative, 8; *P-R* interval, 0.2 second or more, 16; premature beats, ventricular, 2; auricular flutter, 1; *P*, split, 2; *R*, notched or thickened, 15.

Of the 8 negative tracings, none showed clinical evidence of any heart damage and all recovered except 2, both of these were autopsied. One was negative, while the other disclosed cardiac lesions. It will be noted that all the cases of *P-R* conduction were those of various types of myocarditis, and most of them developed abnormal variations in the tracings. The slowest conduction time was 0.24 second. There was one auricular flutter in which the auricles were beating 300 times a minute and the ventricles 150. The patient died with every clinical evidence of a failing circulatory function. We also find evidence of myocardial insufficiency in the abnormal deflection of the *T* and in the notching of the *R*. In other words an examination of Table I, and its comparison by hospital numbers with Table II, will disclose that nearly all of these abnormal electrocardiograms are confirmed by clinical examination. There are five exceptions which will be discussed later.

Electrocardiographic abnormalities are often transient, particularly when they occur in acute diseases, the structural changes which appear in these diseases are likewise often temporary. Whether the electrocardiographic changes are directly dependent upon the structural changes is difficult to determine. In chronic diseases the electrocardiographic changes and the structural changes are generally permanent. It is believed that the electrocardiographic abnormalities mentioned are evidence of structural heart disease, and it would seem wise to treat the patient who presents

them as if his myocardium were attacked by the disease from which he is suffering.

In spite of the fact, however, that in nearly all the abnormal graphic tracings, there is evidence of a corresponding myocardial change, it is nevertheless true, as shown by Cohn, Jamieson, and Frazer,[8] that digitalis can prolong the *P-R* interval, and also modify the *T* wave. Practically all observers believe that inversion of the *T* complex, particularly in the first and second leads or in all three leads, means cardiac muscle damage. The great majority of our cases received digitalis during the course of their illness, so that the value of the abnormalities in the conduction centers, and also the change in the form of the *T* complex, is greatly lessened. We have included these in our tracings because of the interest believed to exist in the comparison between the clinical and electrocardiographic findings, and also because of the fact that in but few cases of a cardiovascular investigation, with muscle damage, can we exclude those who have not had more or less digitalis.

Now, turning to the purely clinical aspect of the circulatory apparatus of our series. In nearly all of these cases blood-pressure readings were taken several times daily with the object of noting Gibson's[6] ratio of millimeters of mercury of the systolic pressure to the cardiac rate. He says: "A pressure appreciably below the normal in pneumonia, is invariably of evil omen, and any considerable fall bodes disaster. When the arterial pressure expressed in millimeters of mercury does not fall below the pulse rate, expressed in beats per minute, the fact may be taken as of excellent augury, while the converse is equally true." The value of this from a prognostic point of view, has been somewhat discredited during the past few years, particularly by Newburgh and Minot.[7] From the result of their observations, they conclude that the prognostic information based on the relation of the systolic pressure to the curve of the pulse rate is more often incorrect than correct.

There were 31 cases in which this was positive, that is, the millimeters of mercury in systolic pressure were definitely below the pulse rate. Of these 16 died, practically all with a diagnosis of cardiac damage. Of the 15 that lived, 9 were clinically rated as having heart pathology. Therefore of the 31 cases there were only 6 in whom a diagnosis of myocardial damage was not made.

Arrhythmia occurred in 6 cases. All but 1, the auricular flutter previously referred to, were premature beats, and of these 2 were classified as of ventricular origin, the others of auricular. Two of this group died; both were believed to have cardiac muscle degeneration. One was autopsied and showed an acute myocarditis with a small amount of pus in the pericardium and pleura. Arrhythmia before the crisis, is regarded by Mackenzie as a very ominous sign. He believes that in all cases of lobar pneumonia showing even an occasional irregularity the prognosis is extremely bad.

TABLE I.—ELECTROCARDIOGRAPH FINDINGS.

Case. No.	Ventricular preponderance.	T, abnormal deflection.	*P–R*, 0.2 second or over.	Notch of *R*.	Auricular flutter.	*P*, split.	Premature beat, ventric.	Negative.	Clinical diagnosis.—Remarks.
6856			0.28			1			Heart sounds poor; first sound flapping; occasional premature beat; P^2 poor; myocardial damage; patient died
7982			0.20	1					As disease advanced every sign of failing heart; blood pressure collapse; myocardial pathology; first sound very weak; pulmonary edema
7409								1	There is apparently no evidence of cardiac pathology, clinically
6309								1	No abnormality could be discovered clinically in the heart
7400		1	0.20						At first, clinical evidence rather slight of cardiac damage, but as disease progressed this became more evident; poor muscle tone
7341				1					Clinically patient became more and more toxic; cardiovascular apparatus is seemingly negative; no evidence of myocardial involvement
7387								1	Showed clinical evidence of muscle damage, also at autopsy
7519			0.20	1					Marked involvement of heart clinically; autopsy showed acute dilatation of heart and parenchymatous degeneration of heart muscle
6544	Left		0.20	1					When admitted to the hospital the cardiac rate was rapid, heart otherwise negative; there were three electrocardiographs taken; first showed probable muscle damage, the other two marked improvement
7943			0.20	1					In this case no clinical sign of myocardial damage; there were two electrocardiographs taken; abnormal complexes in the first, second negative.
6344	Left			1					Clinically and graphically a diagnosis of myocarditis made; there was marked toxemia; the autopsy showed an acute cardiac dilatation, and parenchymatous myocarditis
7413								1	No evidence clinically or graphically of myocarditis
6876			0.20	1		1			No evidence clinically of heart damage; three electrocardiographs taken; first some evidence of muscle abnormality, the last two were negative
7250		1		1					Patient developed encapsulated pus in the lung; during first part of the disease, heart seem to be in excellent shape, but later there was evidence of myocarditis, clinically and graphically
5774								1	The heart remained excellent throughout the disease
5704				1					There was apparently heart involvement, this however rapidly cleared; two electrocardiographs taken, the first showed abnormality, last negative

7700			0.20	1			1		At the onset of this case there was clinical myocardial damage; apparently much improved in a week
5138		1	0.20						This patient showed evidence of cardiac muscle injury later; upon admission no such evidence
5142	Left			1					Undoubtedly a progressively advancing damage of heart, later a gradual improvement, and approach to normal; two electrocardiographs taken
5854	Left		0.20						First few days clinical signs of muscle involvement, this substantiated by graphic tracings; heart improved rapidly; four tracings
6003			0.20	1					Clinically slight impairment of heart muscle; electrocardiograph seems to prove this; later very definite improvement; two electrocardiographs taken
7072								1	This man died; there was no evidence clinically or graphically that myocardium or rest of heart involved; at the autopsy, heart negative
5813					A–300 V–150				This patient showed every evidence of cardiac involvement, both clinically and graphically; two electrocardiographs taken up to the time of death
6123								1	Apparently heart negative; three electrocardiographs taken and all negative
6023								1	Nothing found clinically or graphically wrong with the circulatory apparatus; four electrocardiographs taken
7322				1					This patient started out with an apparent cardiac involvement, but improved rapidly
7953	Left		0.20	1					Clinically there was a suspicion of muscle impairment, and this seems to be confirmed by electrocardiographs
6564	Right	1	0.20	1					In this case the heart appeared to be normal, but the blood pressure was low; in both electrocardiographs muscle damage seems evident
5367		1	0.20						This patient shows typical clinical involvement of the heart; two electrocardiographs taken
5213	Left		0.20					1	A very definite myocarditis, clinically and graphically; three electrocardiographs taken
6158			0.2 to 0.24						This patient did not show a clinical myocarditis; two electrocardiographs, however, pointed to a slight delay in conduction
	Right, 6 Left, 6	5	16	15	1	2	2	8	

TABLE II.

Systolic blood pressure (−) and pulse rate (+):								
Living	6158	6544	7700	7691	6123	7322	6771	6564
	7413	7877	6602	6023	7097	7953	7707	
Dead	5489	8164	7519	8477	7213	6172	5539	7952
	5138	6084	6856	7387	7451	5813	4269	6344
Arrhythmia	5489	7700	5213					
	5843	6856	5813					
Poor sounds, cardiac:								
1st	5539	5357	5213	8164	6856	7982	7707	7400
	7387	7519	6344	6226	7260	7451	8477	6721
	5679	7700	6602	5138	5142	5843	5813	6084
	4209	7322	7953	8477				
P^2	5539	5357	5213	7982	7707	7519	6226	7451
	8477	6721	6602	5843	5813	4269		
A^2	5357	5213	8164	7707	7519	7451	8477	6721
	5679	6602	5142	5843	4269			
Cardiac murmurs	5539	8825						
	5213	6721						
Pulmonary edema	5357	8164	7982	6344				
	5138	5813	6084					
Clinical myocardial damage:								
Living	5213	7707	6721	7700	6602	5843	7953	
	5545	6544	5704	7691	5142	7322		
Dead	5357	5539	6856	7982	7387	6344	7260	5138
	6084	8164	7400	7519	6226	7451	5813	8477
E.K. negative	7387							
Graphic Myocardial change:								
Living	5213	6158	5704	6602	5843	7953		
	6544	6876	7700	5142	6003	6504		
Dead	5357	6856	7400	6344	5138			
	7982	7519	7260	5813				
Clinically negative	6544	6876	6564					
	6158	6003						
No circulatory damage, clinically or graphically	5377	8169	6309	7493	7877	7213		
	7307	7409	7330	7413	6955	6023		
	6752	6379	7341	6824	7072	6771		
	4666	5042	5774	6123	4507			
Reduplication of sounds	5213							
Cardiac increase to left	7982	8477	6602	7096	7400			
	8825	5142	7097	7451	6721			
	5843	6771						
Gallop rhythm	6602							
Cyanosis	5357	7877	5142	6084				
	7715	5138	5813					

The group "poor sounds," classified on Table II as "poor sounds, cardiac," is one of the largest, and includes a study of the first sound and the aortic and pulmonary sounds. In estimating the quality of the valve closure, plus the muscle tone of the first sound, and the purely valvular quality of the other two, it is admittedly and notoriously difficult to gauge their values and to establish a standard, nevertheless an attempt was made to tabulate them according to weakness, feebleness and loss of muscle quality. Of these the first sound was mentioned as weak, feeble or flapping in 28; the aortic and pulmonary as diminished or weakened in 32. Nineteen of this group died and most of them showed marked and definite symptoms of other clinical signs of myocarditis.

Cardiac murmurs were found in 3 patients, 1 of whom died and was autopsied. A myocarditis was discovered, and microscopic sections showed the muscle fibers much swollen and partly obliterated with a granular degeneration of the protoplasm. Nothing of note was seen in the endocardium, in spite of the fact that a systolic murmur was heard during life. In the other 2 the murmur was also systolic in time, but in the 1, it disappeared as the patient became better, while in the other there was clear evidence of an old cardiac hypertrophy, so that a chronic endocarditis was probably present previous to the pneumonia. It is not believed that the endocardium was acutely involved in the present series, and this is in accordance with the generally accepted view of most observers that this structure is not usually severely injured in this type of infection, the brunt of the attack being probably sustained by the myocardium and pericardium.

Pulmonary edema, believed to be due in most instances to gradual failure of the right heart, was found in 7 cases, and is of extremely bad prognostic omen, for all these patients died. Two were autopsied, and in 1 acute dilatation of the heart and parenchymatous myocarditis was reported with microscopic findings of the muscle fibers considerably swollen, and in some areas the disappearance of their cross striations. The other showed gross muscle softening and degeneration, the microscopic study revealing in a few places the muscle protoplasm finely granular with a loss of striation.

The 5 remaining cases, although the heart was not examined pathologically, showed clinical evidence of a degeneration and failure of the heart muscle. We believe therefore, that we are right in assuming pulmonary edema to be due primarily to a failure of the cardiac function, particularly of the right heart, and is accompanied in most instances by a weakness or feebleness of the pulmonary valve sound.

The diagnosis clinically of myocarditis from a combination of the physical signs previously discussed, (exclusive of graphic tracings), was made in 29 cases; of these 16 died and 3 were autopsied, all of them revealing definite evidence of muscle pathology, both clinically and microscopically.

Myocardial insufficiency was diagnosed in 21 patients from graphic tracings, many of these were confirmed clinically, and most were duplicated in the clinical grouping; but 5 cases were not, that is, they were negative regarding cardiac pathology from a clinical view point; the electrocardiograms showed deviation from the normal. This is interesting, so that a short résumé of each case according to hospital number will be given. These findings were as follows:

Patient No. 6544: Slightly delayed conduction; left preponderance of muscle mass; notching of *R*, three tracings taken.

Patient No. 6876: Conduction time, two-tenths second; wide

deflection of *R* Lead II; *P* bifurcated Lead I; three tracings were taken.

Patient No. 6564: Conduction time, two-tenths second; notching *R* Lead III; right preponderance of muscle mass; *T* inverted Lead I; two tracings were taken.

Patient No. 6158: Conduction time, twenty-four hundredths second.

Patient No. 6003: Notching of *R*, and conduction time two-tenths seconds; two tracings were taken.

No cardiovascular pathology could be discovered clinically or graphically in 23 cases. All of them recovered except 5, and of these 3 were autopsied. In 1 the heart showed nothing of importance and death was probably due to a pneumococcus meningitis, another did not reveal any gross cardiac pathology, but microscopically showed muscle degeneration, while in the third, a patient dying five hours after admission, the muscle was apparently absolutely normal, both macroscopically and microscopically. In the 2 observed only clinically, in 1 the heart condition did not reveal marked or even moderate abnormality, the muscle tone was excellent, and there were no adventitious sounds. He became more and more toxic, but the heart did not fail until nearly the last. The other one died forty-eight hours after admission, was extremely toxic, but did not show any definite sign of cardiac involvement.

There was only 1 case of reduplication of the heart sounds, the second. This patient was very sick, with poor muscle tone, irregularity of rhythm and a systolic murmur. Electrocardiogram proved also a muscle deficiency. Therefore a definite myocarditis was believed to be present, both clinically and graphically. There was a left ventricular preponderance, conduction time two-tenths second, and several premature beats of ventricular origin. The patient recovered.

Increase of the transverse area of the heart to the left was difficult to make out, because of the frequent pulmonary involvement on the left side, but this was presumed to be present in 12 cases. Four of these cases died, and all of them pointed conclusively to cardiac failure. There was only 1 autopsy in this group, and the findings in it showed heart muscle degeneration. This widening of the transverse area of the heart was undoubtedly due in some of the cases to right ventricular dilatation, for 6 of these 12 were accompanied by a weak pulmonary second sound.

Gallop rhythm was recognized once, and occurred in a patient who developed a pneumonia following a delivery. She was progressing satisfactorily in every way when there developed a sudden cardiac collapse with marked substernal pain, moist pale skin, extremely low blood pressure (systolic, 80; diastolic, 40), rapid and nearly inaudible heart sounds, which soon developed into the characteristic gallop rhythm. This patient recovered.

Among the most frequent signs of heart failure, particularly of right heart failure, are cyanosis and dyspnea. Both of these are frequently present from the start of a pneumonia which is apparently progressing favorably, and it is probable that all cases of this disease, have one or the other, at some time during the infection. The attempt was made, however, to identify marked and noticeable signs of cyanosis, particularly when more or less generalized. There were 7 of these cases and 5 of them died. All except 1 showed unmistakable signs of cardiac failure, and that 1 died so quickly after entering the hospital that no definite opinion could be given. Of the 2 that recovered, 1 gave every evidence of cardiovascular injury; the other did not seem very ill, and the only evidence of circulatory disturbance was hypotension.

In pneumonias of various grades pericarditis seems to be extremely common. It is difficult to discover clinically, particularly when the left side of the lung is involved, but should always be kept in mind and repeatedly looked for. In Berry's report of 400 autopsies 25 per cent showed involvement of the pericardium, while Feinblatt in his series of 180 cases of both lobar and bronchopneumonia finds 20 per cent of pericardial pathology.

In our series of 16 autopsies there were 3 cases of pericarditis, 2 contained pus and 1 was fibrinous. There was 1 case which recovered upon which a clinical diagnosis of fibrinous pericarditis was made. This patient developed an empyema following his pneumonia, and was septic for a long time. He ultimately recovered. All the autopsied patients revealing pericarditis showed both gross and microscopic damage to the heart muscle. Our series therefore presents 4 cases of pericardial involvement, making 25 per cent, a figure corresponding very closely with the larger series.

Summary. The cardiovascular apparatus in 78 cases of lobar pneumonia and bronchopneumonia was studied.

Sixteen patients were autopsied, resulting as follows: Pericarditis with effusion, 1; pericarditis, fibrinous, 1; pericarditis, purulent, 1; chronic endocarditis, 2; myocarditis, 14; acute dilatation, 5; negative, 2. In nearly all the cases blood pressure readings were taken. There were 31 patients in which the millimeters of mercury in systolic blood pressure were definitely less than the pulse rate. Over half of these patients died, and of those that lived there were only 6 in which the diagnosis of myocarditis was not made.

Arrhythmia occurred in 6 patients, 2 died. The irregularity in all but 1, was premature beats.

Weak or feeble heart sounds were mentioned in 32; 19 of this group died.

Only 3 cardiac murmurs were discovered.

Of the 7 patients who developed pulmonary edema, all died.

A clinical diagnosis of myocarditis was made in 29 cases, 16 died and 3 were autopsied, all of whom showed damaged muscle.

Myocardial insufficiency was diagnosed in 21 patients from graphic tracings, most of them being confirmed clinically.

No cardiovascular disturbance could be discovered in 23 cases. All recovered except 5. There were 3 autopsied, and 1 showed cardiac muscle degeneration.

Reduplication of sound was recognized once, and gallop rhythm once.

Cardiac enlargement was discovered in 12, and in 6 was possibly due to right dilatation.

Death in pneumonia is, in the large majority of cases, one of cardiac failure.

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THE GRAPHIC PRESENTATION OF THE BLOOD SEDIMENTATION TEST.

A Study in Pulmonary Tuberculosis.

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Every physician who has the responsibility for the care of tuberculous patients knows how difficult it is to guide the patient through the various stages of his illness, and how cautious he must be in prescribing rest and exercise, because of the uncertainty that is felt in estimating activity. Judgment is difficult and must be attained by careful observation of each case and finally by the experimental method of testing the patient's reaction to small allotments of exercise. "Everyone has had the experience of failure in preventing relapses during treatment and all have diligently sought the method which would restore the invalid to an earning capacity in the shortest possible time."[1] Many workers in tuberculosis have employed the blood sedimentation test and report that it offers a valuable help in the estimation of activity. It was with the hope of adding something to our knowledge of its clinical value that this study was undertaken.

Clinical Classification of Pulmonary Tuberculosis. One of the earliest problems that presented itself was the adoption of a satisfactory clinical classification of pulmonary tuberculosis, for it was felt that a true estimation of the sedimentation test must depend largely upon how closely the clinical classification parallels the course of the disease. Any classification of tuberculous patients must of necessity be arbitrary, for tuberculosis as a disease is different and distinct from any other. The designations commonly employed such as "disease arrested" and "apparently cured," are only relative terms, because the patient must always remember that he is harboring an infection which may be awakened into activity at the first opportunity.

The following classification which is based largely on those adopted by the National Tuberculosis Association and the American Sanatorium Association is not offered as a substitute for existing systems but for the purpose of showing more clearly the results obtained.

CLINICAL CLASSIFICATION OF PULMONARY TUBERCULOSIS.

I. ACTIVE.
1. Slight.
2. Moderate.
3. Marked.

II. INACTIVE.
1. Apparently quiescent.
2. Quiescent.
3. Apparently disease arrested.
4. Disease arrested.
5. Apparently cured.

Clinically Active Tuberculosis. Just what is meant by activity will probably be open to debate for many years. For the purposes of this study, it is perhaps better to think of pathologic activity and of clinical activity and to regard these as two separate phases of the same process. Pathologic activity may be defined as "that stage of a tuberculous process in which some change is taking place, whether progressive or retrogressive."[2] Clinical activity is the outward manifestation of pathologic activity and may or may not be present. When it is present, as witnessed by constitutional symptoms, it always implies pathologic activity. But just as certain as there can be fire without smoke, so there can be pathologic activity without clinical activity. Indeed, retrogressive pathologic activity can continue long after all evidence of clinical activity has vanished.

All patients with constitutional symptoms were regarded as clinically active. In a purely arbitrary way these patients were further subdivided into slightly, moderately and markedly active groups, depending upon the severity of the constitutional symptoms.

By constitutional symptoms are understood the following: (1) Temperature of 99° F. or more; (2) pulse rate of 90 or more; (3) symptoms of toxemia such as lack of appetite, malaise, night sweats,

lack of endurance, loss of weight and loss of strength; (4) presence of blood spitting or pleurisy.

Clinically Inactive Tuberculosis. All patients free from constitutional symptoms were considered clinically inactive in accordance with the following scheme:

1. Apparently quiescent: Absence of all constitutional symptoms; cough, expectoration and bacilli may or may not be present; the foregoing conditions to have existed for at least two weeks.

2. Quiescent: Absence of all constitutional symptoms; cough, expectoration and bacilli may or may not be present; the foregoing conditions to have existed for at least two months.

3. Apparently arrested: Absence of all constitutional symptoms; cough, expectoration and bacilli may or may not be present; the foregoing conditions to have existed for at least three months under graduated exercise.

4. Disease arrested: Absence of all constitutional symptoms; cough, expectoration and bacilli may or may not be present; the foregoing to have existed for at least six months, under conditions approaching those of normal life.

5. Apparently cured: Absence of all constitutional symptoms, along with cough, expectoration and bacilli for a period of two years under ordinary conditions of life.

The Blood Sedimentation Test. With this introduction to the nature of the problem to be investigated we can now turn our attention to the blood sedimentation test. The sedimentation phenomenon is a nonspecific reaction of citrated blood, manifesting itself by striking differences in the rapidity with which red blood cells sediment, being much slower in health than in disease. The test consists in observing the rapidity with which the red blood cells settle out from the plasma. In healthy individuals the rapidity of sedimentation varies within certain limits, just as the leukocyte count and pulse rate. Compared with the findings in healthy men, it is increased in the newborn, in the aged, in women and during menstruation.

Historical. The hastened settling of inflammatory blood has been known to physicians for centuries and was considered a particularly important clinical sign, both theroretically and practically. With the ceasing of blood-letting and the disrepute of humoral doctrines because of the advent of cellular pathology, it practically has become forgotten. And now observed again independently by modern investigators, it appears with a new meaning and in a new light.

Many writers credit Galen as the first to call attention to this phenomenon under the name of crusta phlogistica. John Hunter studied the phenomenon of blood sedimentation in 1791. "He not only observed that the erythrocytes during an inflammatory process settled more quickly in their own plasma, but he was also

the first to demonstrate that the red blood cells of normal blood, when separated and transferred to the plasma of inflammatory blood, settled with greater speed, the rapidity of this process being in direct relation to the severity of the infection."[3]

Almost a hundred years later John Ashhurst used to teach that the blood in inflammatory conditions showed the following change: "Owing to the changes in the constitution of the blood in inflammation, its mode of coagulation differs from that of blood in normal state. The crassamentum or clot forms more slowly than in health, and is smaller and firmer in consistence. The slowness of coagulation and the *increased cohesiveness* of red corpuscles allow the separation of the fibrin and white corpuscles to take place before the process of clotting is completed, and this gives rise to the peculiar appearance which is known as the buffy coat."[4] The buffy coat is apparently Galen's crusta phlogistica.

In 1918 Fahraeus[5] rediscovered the phenomenon of blood sedimentation in pregnancy and started the present wave of investigation. It has since been observed and studied in tuberculosis, cancer, various forms of joint disease, pneumonia, scarlet fever, acute infections in general, pelvic inflammatory disease, syphilis, anemia, psychosis and many other conditions. But an intelligent comparison of the results obtained is difficult, and leads only to confusion, since various workers have used different methods and recorded their results in different units. Practically all, however, have found it of clinical value.

Theory. It is not within the scope of this paper to discuss the various theories advocated to explain this interesting phenomenon. It is safe to say, however, that out of the host of theories propounded, from autoagglutination, electrophysical reaction, increased fibrinogen content of blood plasma, down to the presence of some specific something (ferment) in the plasma, there is not one universally accepted explanation. Regardless of theory, the ultimate cause apparently depends upon the degree of cellular destruction going on in the body. The sedimentation reaction is generally regarded as a measure of pathologic activity and therefore as a symptom of an entirely general kind. It is a fine quantitative measure of the change in the blood, produced by a destructive process somewhere in the body. It does not diagnose nor does it localize the infection. It does not indicate the state of the diseased organ, but it does reflect the disturbance produced in the organism through the absorption of products of infection.

Technique. Three principal methods have been developed for performing this test, and each has many modifications. Each method is relatively simple and all give valuable information But an intelligent comparison of the results obtained is all but impossible. To fully appreciate this, and to emphasize the need of a satisfactory standard technique, the various methods will be briefly reviewed.

For the sake of clearness, they will be referred to as the distance, time and graph methods, depending upon the manner in which the results are recorded.

The Distance Method. The underlying principle of the distance method is noting the distance through which the red blood cells sediment in a given time, and recording the results in millimeters. This method is the oldest, and was first advocated by Fahraeus.[5] It has since been modified by various others. The Westergreen[6] modification is the one most commonly employed, and the distance method is often referred to as the Westergreen method, the essential points of which are as follows:

Pipette tubes 300 mm. in height and 2.5 mm. in diameter are used, with a mark 200 mm. from the bottom of the tube. One part of 3.8 per cent sodium citrate solution is mixed with 4 parts of blood. After gentle agitation, the mixture is poured into the tube, up to the 200-mm. mark. The height of the supernatant fluid column is measured after one hour, two hours and twenty-four hours. The level attained by the red cells in twenty-four hours, simply gives a rough idea of their number. In healthy men the supernatant fluid column after one hour measures 3 mm., in women 5 to 10 mm.

There are two outstanding modifications of the distance method which should be mentioned. To reduce the time factor involved in carrying out this test Henkel[7] suggested that the blood be centrifuged for five minutes at a speed of 1100 revolutions per minute, and then note the degree of sedimentation, recording the results in millimeters. Henkel has shown that a definite relationship exists between his method and the much more time consuming Linzenmeier method to be described.

Fischel,[8] using Westergreen's technique, expresses his results in percentage instead of millimeters, for he is convinced that the "only factor which really matters is the height of the whole column, and that the percentage is a true expression of the sinking velocity," He observes the column of supernatant clear fluid as does Westergreen, but instead of expressing his results in absolute figures, "brings them into relation to the height of the whole column, by calculating the height of the clear column in percentage of the whole suspension column."

Numerous other modifications have been advocated but they have to do chiefly with the size of the tube, amount of blood used, and the degree of dilution.

The Time Method. The time method of studying the sedimentation reaction is the direct opposite of the distance method. In the distance method, one fixes the time and measures the distance recording the results in millimeters, while in the time method, one fixes the distance and observes the time, recording the results in minutes. The time method of studying the sedimentation reaction was first advocated by Linzenmeier,[9] and is called the Linzenmeier method. Its essential features are these:

Small tubes of 5 mm. diameter, 6.5 cm. in height are used, with two marks, one at the level of 1 cc. and the other 18 mm. below this. One part of 3.8 per cent sodium citrate solution (0.2 cc.) and 4 parts of blood (0.8 cc.), are aspirated into a properly calibrated syringe, gently mixed and poured into the tube up to the 1-cc mark. The tube is then allowed to stand upright and the sedimentation time, that is the time required for the upper level of the red cells to reach the 18-mm. mark is determined. The results are expressed in minutes.

The normal sedimentation time for healthy men is from twelve hundred to fourteen hundred minutes, for healthy women from eight hundred to ten hundred, and during menstruation it is sometimes six hundred. Anything under two hundred is usually regarded as pathologic.

The time method also has numerous modifications, but as in the case of the distance method, they are of minor importance. Recently Linzenmeier among others, has recommended that a millimeter reading be taken at the end of the hour and the sedimentation time be observed as usual. Baer and Reis[10] used both readings in their studies.

Objections have been raised to both the time and distance methods. It is claimed that the Westergreen method is not accurate because it involves the use of long tubes of small caliber that cause great error in the results because of capillary attraction and friction between the cells and the walls of the tube. On the other hand, the time method as advocated by Linzenmeier is tedious and time consuming and is hardly practical as a routine procedure in an institution. Furthermore, it gives no more information than the less time consuming Westergreen or distance method.

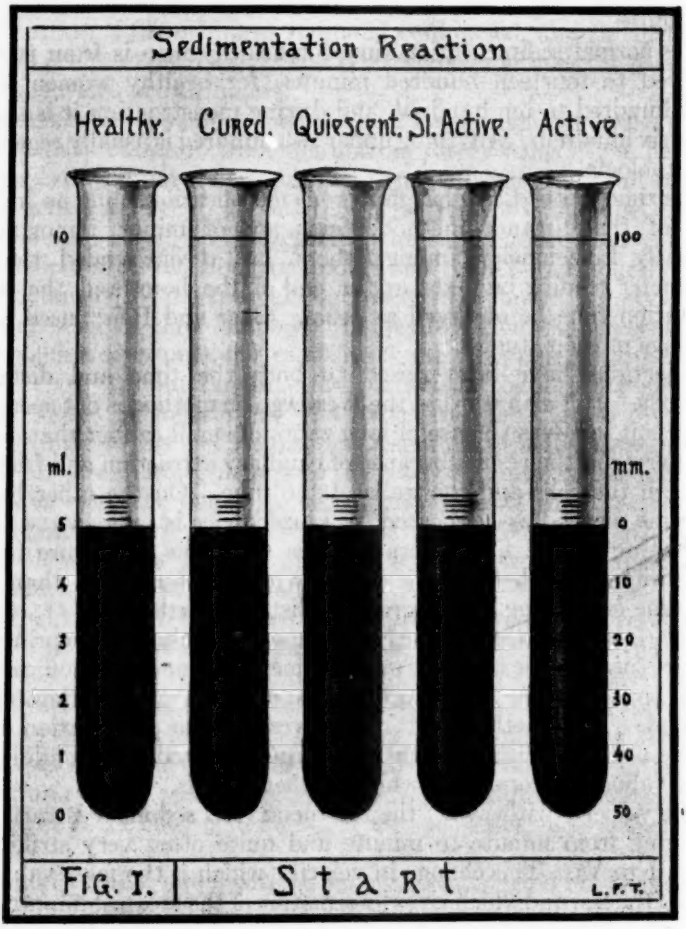
The Graphic Method. The graphic method embodies the principal features of both the time and distance method, but differs sufficiently from both of these to be properly spoken of as an independent method. This method not only gives all the information that can be obtained from the time or distance method, but in addition, gives valuable information which neither reveals.

The velocity with which the red blood cells sediment is variable, changing from minute to minute and quite often very strikingly (Figs. I to V). This change in velocity which is the most valuable part of the test and which gives information of the greatest importance clinically, is completely lost and not recorded in either the distance or time method. To study the sedimentation reaction, therefore, by either of these methods is only studying one phase of the reaction, the end result.

For many of the details here described, the author is greatly indebted to Poindecker[11] and Gilbert and Tzanck[12] from whose papers he has received invaluable suggestions and ideas. The only essential apparatus required is a special sedimentation tube

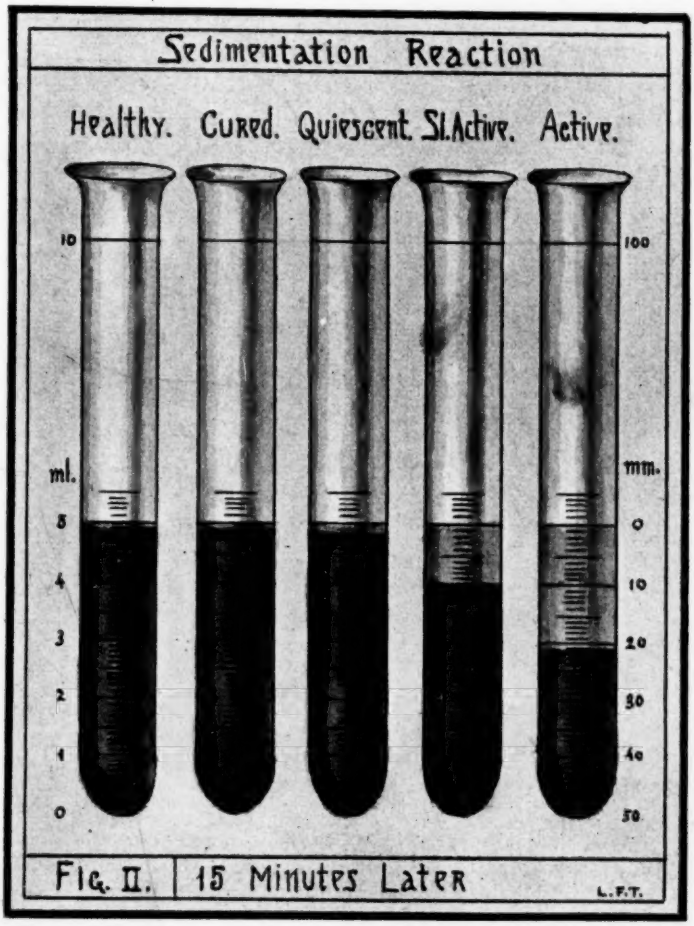
of at least 5-cc. capacity, graduated into tenths of a cubic centimeter, each 1 mm. in height and marked in millimeters. I have had tubes made which meet these specifications, and which can be readily procured from Arthur H. Thomas Co., Philadelphia, Pa.

Other desirable apparatus is as follows: (1) A 5-cc. syringe graduated into 0.5-cc. divisions; (2) sharp needles, preferably 20-gauge;



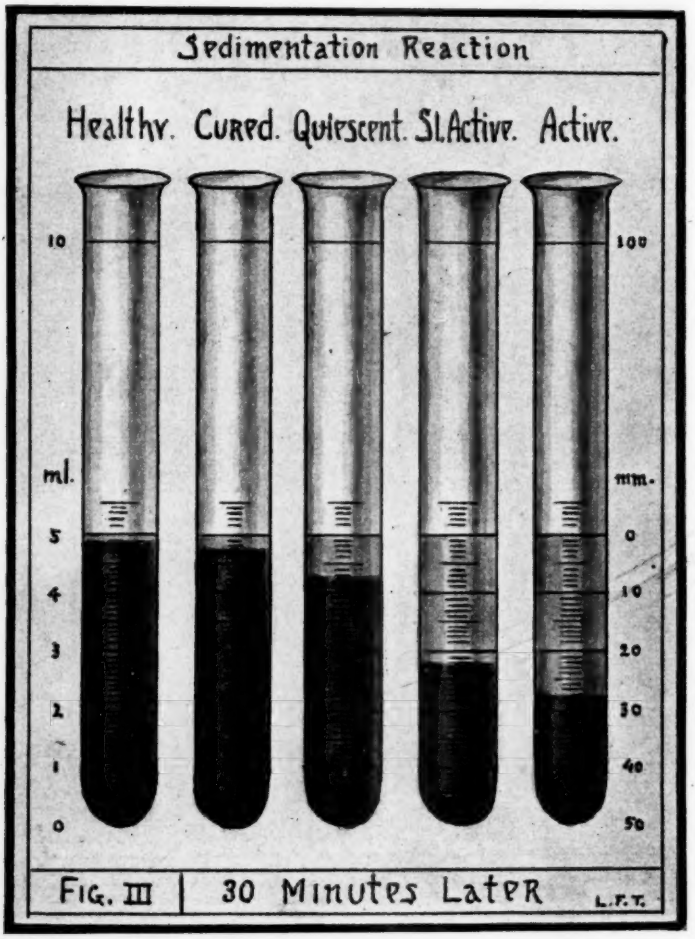
(3) freshly prepared 3 per cent sodium citrate solution, to prevent clotting of blood; (4) special sedimentation charts for recording observations (Fig. VI). These charts can be obtained from Charles M. Berkemeyer, Sellersville, Pa.; (5) a rack for holding sedimentation tubes; (6) several small basins for water, alcohol, sponges, and so forth.

Procedure. Cleanliness and dryness of apparatus is essential. If any clotting occurs, the test must be done over: (1) Apply tourniquet to arm. (2) Aspirate into syringe 0.5 cc. of 3 per cent sodium citrate solution. (3) Puncture cubital vein and draw blood to 5-cc. mark. (4) Release tourniquet and withdraw needle from vein. (5) Draw back the barrel of the syringe about 1 cm.



and gently tilt the syringe backward and forward several times to insure uniform mixing of blood and citrate solution. (6) Remove needle from syringe, as it may contain clotted blood, and pour contents into the sedimentation tube. (7) When it is necessary to obtain specimens from several patients, let this tube stand in the rack without paying any attention to it. (8) Wash syringe in water, wipe barrel with a clean cloth and then pass syringe through

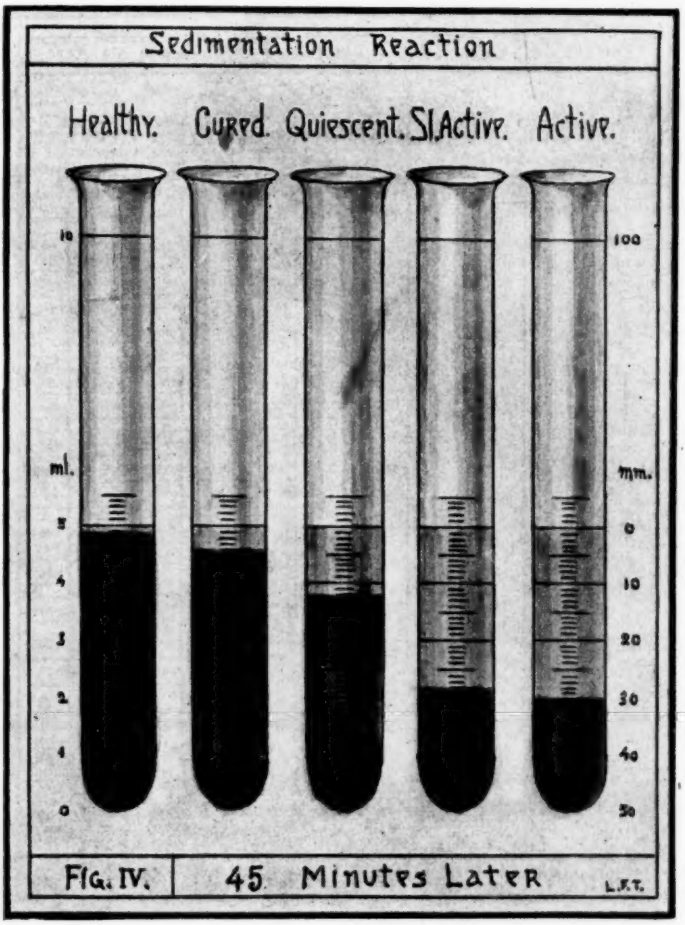
alcohol and ether and dry in air; this insures a clean and dry syringe, which is again ready for use. (9) After all the samples of blood have been taken they are carried to the laboratory; it is best to number each tube to avoid possible error, and to carry the tubes in a rack. (10) Before any readings are made each tube is stoppered with a paraffin coated cork and gently turned upside down two or



three times; this insures a uniform distribution of the red blood cells, for by the time the tubes are brought to the laboratory, in many cases marked sedimentation has already taken place.

The tubes can be allowed to stand as long as ten hours before making any readings without losing valuable information, or noticing any practical change in the character of the graph. After ten hours the sedimentation phenomenon begins to disappear,

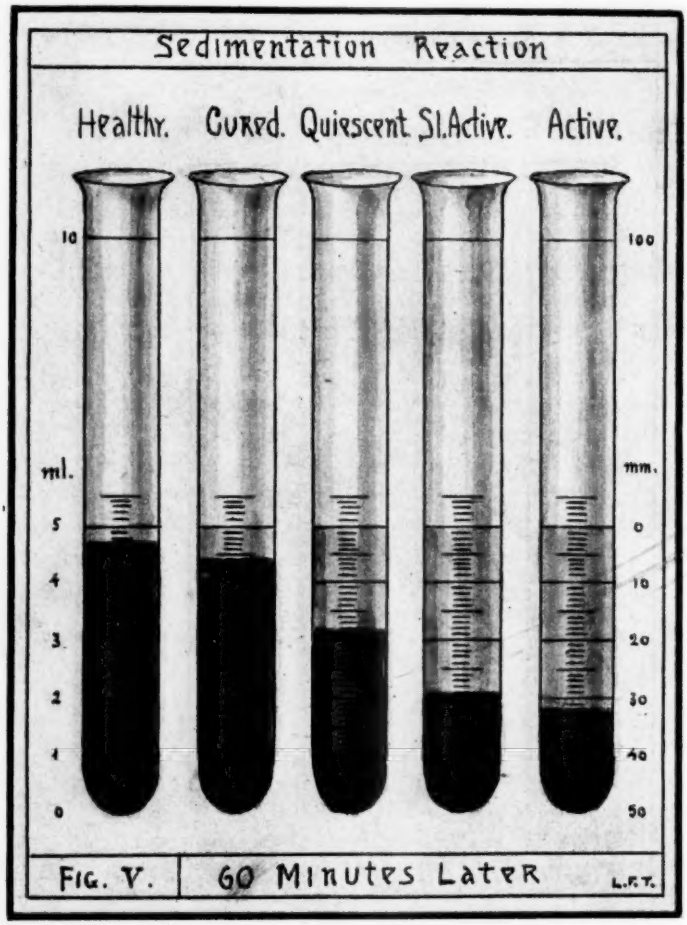
especially in those cases where there has been a marked and rapid sedimentation. This was clearly established through experiment, by repeating the entire set of readings on the same samples of blood at various hours after the initial observations were made. In no instance was there any practical difference where the readings were made within ten hours; it is not safe to wait longer than ten hours.



Recording Observations. The position of the sedimenting column of red blood cells is read every five minutes for one hour. This is done with ease as the boundary zone between the red blood cells and the plasma, is usually sharp and distinct (Fig. I to V). The observations are recorded on the sedimentation charts on which the horizontal lines represent the divisions on the sedimentation tube and the vertical lines, the intervals of time. In this way, a

graph is traced which shows the position of the sedimenting column of red blood cells at any period of time during the first hour (Fig. VI).

The sedimentation value is determined according to the path traversed by the red blood cells during the first hour and depends upon the nature of the graph, the sedimentation index and the sedimentation time. Together they furnish all the information that is



likely to be obtained from the sedimentation test. The graph serves as a rough estimation of the presence or absence of pathologic activity. The sedimentation index and sedimentation time help to determine the degree.

Definitions. As can be seen from Fig. VI there are four distinct graphs, two of which are straight lines and two of which are curves. From the nature of the graph, they are called horizontal line,

diagonal line, diagonal curve and vertical curve. A horizontal line within the meaning of the sedimentation reaction may be defined as a straight line, with a sedimentation index falling within normal limits, and a sedimentation time always longer than sixty minutes. By sedimentation index is meant the total sedimentation of the red blood cells at the end of sixty minutes expressed in millimeters.

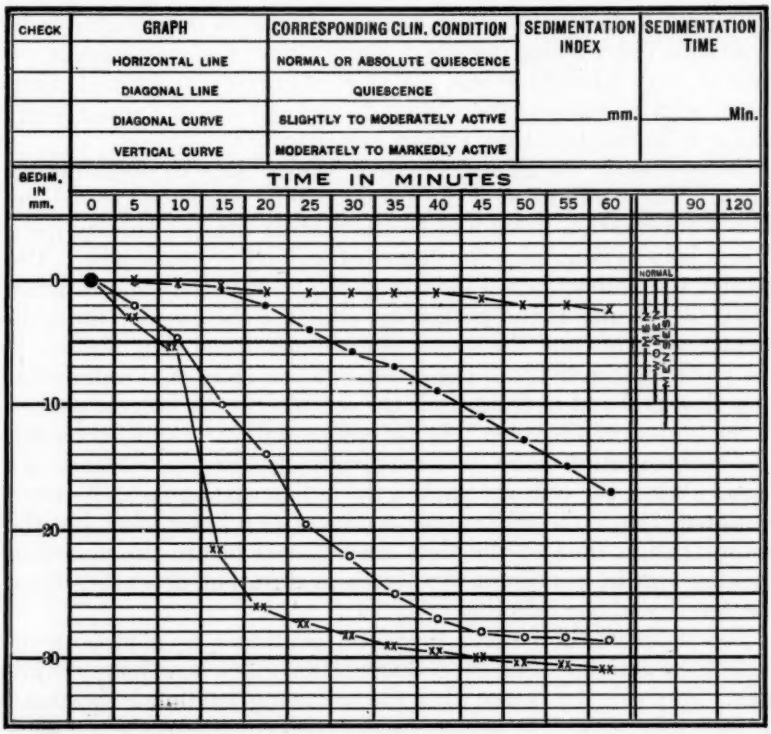


FIG. VI

The graphs are actual reproductions of the sedimentation phenomenon as portrayed in Figs. I to V inclusive.

——×——×—— Horizontal line (clinically healthy individual).
——●——●—— Diagonal line (clinically quiescent tuberculosis).
——○——○—— Diagonal curve (clinically slightly active tuberculosis).
——××——××—— Vertical curve (clinically markedly active tuberculosis).

The normal sedimentation index for men varies from 2 to 8 mm., with an average of 3 to 4; for healthy women from 2 to 10 mm., with an average of 5 to 6; during menstruation probably as high as 12 mm.

Rothe[13] has divided the sedimentation reaction into three distinct phases: (1) Preagglutination period, with slow sedimentation; (2) agglutination period with rapid sedimentation; (3) period of packing, when the sedimentation slows again and finally ceases

because the erythrocytes become packed in the bottom of the tube as closely as possible (vertical curve, Fig. VI).

By sedimentation time is meant the number of minutes that elapse before the period of packing of the red blood cells sets in. The normal sedimentation time is always a question of hours. A diagonal line is a straight line with a sedimentation index falling outside of normal limits and a sedimentation time of sixty minutes or more. A diagonal curve is a curve of gradual slope with a sedimentation index falling outside of normal limits and a sedimentation time of sixty minutes or less. A vertical curve is a curve of sharp slope, with a sedimentation index falling outside of normal limits and a sedimentation time always less than sixty minutes.

Significance of Sedimentation Index and Sedimentation Time. The significance of the graphs will be considered elsewhere. The sedimentation index and sedimentation time as already mentioned help to determine the degree of activity or quiescence. The greater the sedimentation index and the shorter the sedimentation time, the greater is the pathologic activity; the smaller the sedimentation index and the longer the sedimentation time the less is the pathologic activity. The sedimentation index and sedimentation time go hand in hand until the red blood cells become packed in the bottom of the tube. As the sedimentation index is increased, the sedimentation time is correspondingly diminished and *vice versa*. When the cells are packed the sedimentation index becomes stationary, since the cells cannot sediment to a lower level, but the sedimentation time or the time that elapses before the period of packing sets in, continues to shorten in duration, depending upon the severity of the infection (Fig. VI).

The sedimentation time, therefore, continues as a measure of pathologic activity when the sedimentation index is no longer available. As a rule this is true when the sedimentation time is shortened to sixty minutes or less, because under such conditions the sedimentation index has reached its maximum. When longer it yields no information which is not obtained from the sedimentation index. For practical purposes, therefore, the sedimentation time is of value when it is sixty minutes or less, when more than sixty minutes, it need not be determined, especially when the graph is either a horizontal or a diagonal line.

The sedimentation index yields information in addition to that already considered. In healthy individuals the volume of red blood cells after complete sedimentation is about 50 per cent of the total volume of blood. In anemia the volume of red blood cells is naturally reduced. This is reflected in the sedimentation index. When the sedimentation index is unusually high, regardless of the character of the graph, it indicates among other things a small volume of the red blood cells and should always suggest anemia. In this respect the sedimentation index serves the purpose of the hematocrit.

Test Studied under Controlled Conditions. In studying the sedimentation test every effort was made to suppress enthusiasm and to record only facts. With few exceptions all samples of blood were drawn between 9.30 and 11 A.M., and all readings made within one hour at room temperature which was kept practically constant during the entire study. The influences of diet, exercise and even medication were happily eliminated, for the patients in the Sanatorium lived in accordance with a specified regime and under a prescribed diet. For experimental purposes more ideal conditions could hardly be wished for. Patients with complications which might influence the sedimentation reaction were not included in this study as they will form the basis for further investigation. Each patient studied was assigned a serial number which was used in place of his or her name throughout, to avoid possible bias. For each patient studied a special chart was filled out of which the following is a typical example:

CLINICALLY ACTIVE TUBERCULOSIS.

Serial No. Tube No. Date.
Name Case No.
Sex Age Height Dept.
Involvement: R.—L.
Stage (Turban): I—II—III.
Present condition: Good—Fair—Poor.
Cough: None—Slight—Moderate—Severe.
Fever (average past week):
Pulse (average past week):
Expectoration (cc.): Sputum: Positive— Negative—
Weight (pounds):
Highest— Present—
Average— Standard—
Lowest— Percentage above or below standard—
Admission— Percentage above or below highest—
Course: Acute—Chronic—Progressive—Improving—Stationary
Duration of disease:
Duration of clinical activity:
Duration of clinical inactivity;
Clubbed fingers: Yes—No
Curved Nails: Yes—No
Menstruation: Yes—No
Complications:

In addition each visiting physician was asked to state in writing what he personally believed to be the clinical condition of his patient. With this information as a basis and the clinical classification described as a guide, each patient was classified into his or her respective clinical group. The conclusions were recorded on small pieces of paper, each of which had a serial number corresponding to the serial number of the patient. Those falling within the same clinical group were pasted on cardboards.

The results of the sedimentation test were determined from the original graphs, independently and without knowledge of the clinical classification of the patient. The findings were recorded on small

pieces of paper each of which had a serial number, corresponding to the serial number of the patient, the same procedure as was gone through in classifying the patients clinically. Each of these papers were then pasted on the cardboards opposite the corresponding serial numbered paper bearing the clinical classification of the patient. In this way the clinical condition of the patient was matched with the sedimentation test.

Significance of Graphs. The findings for each clinical group were tabulated with the results. (See page 897.)

I regret that opportunity did not present itself to study the reaction in a larger number of healthy individuals, but I believe that I have a sufficient number to permit a tentative statement, especially after reviewing and correlating the results of others and finding that they are in agreement.

In healthy individuals the graph is always a horizontal line. The only variable factor is the sedimentation index or the total sedimentation of the red blood cells at the end of sixty minutes. Compared with the findings in men, the sedimentation index is greater in women and during menstruation. The normal values have already been mentioned.

In clinically active tuberculosis, with very few exceptions, the graph is either a diagonal or a vertical curve, depending upon the severity of the infection. The diagonal curve is obtained chiefly in slight to moderately active tuberculosis, while the vertical curve is obtained chiefly in moderate to markedly active tuberculosis. At times a diagonal line may be obtained in clinically slightly active tuberculosis, but it is almost invariably of high sedimentation index.

In this study are included 65 cases of clinically active tuberculosis. In 7, all of whom were slightly active, the graph was a diagonal line, but of high sedimentation index. In all the others, the graph was either a diagonal or a vertical curve. The percentage of those with vertical curves was materially increased in the more active groups. Likewise the sedimentation time or the time that elapses before the period of packing sets in became shorter the more active the disease.

In the apparently quiescent and quiescent groups the findings range all the way from vertical curve to horizontal line with the majority yielding diagonal lines. On first thought it would seem as though the test has fallen down. Indeed, it is just the reverse. The very fact that there are no constant findings proves the value and practicality of this test. When it is considered that in these groups are patients who have been free from constitutional symptoms for a period varying from two weeks to two months from the date of admission to the Sanatorium and that the type of patient included varies from the problematical to the far advanced with a temporary period of quiescence, it is very readily understood why there should not be constant findings if the test is a true index of pathologic activity.

Clinical classification.	Number of cases.	Graph.				Sedimentation index, (mm.).						Sedimentation time. (minutes).			
		Horizontal line.	Diagonal line.	Diagonal curve.	Vertical curve.	<10	<15	<20	<25	<30	<35	<15	<30	<45	<60
Healthy	17	17 / 100%				17 / 100%									
Apparently cured	11	10 / 91%	1 / 9%			10 / 91%			1 / 9%						
Disease arrested	20	7 / 35%	11 / 55%	2 / 10%		7 / 35%	6 / 30%	3 / 15%	2 / 10%	2 / 10%					2 / 100%
Disease apparently arrested	12	5 / 42%	6 / 50%	1 / 8%		5 / 42%	3 / 26%	2 / 16%	2 / 16%						1 / 100%
Quiescent	58	6 / 10%	32 / 55%	16 / 28%	4 / 7%	6 / 10%	6 / 10%	13 / 23%	19 / 33%	14 / 24%			1 / 5%	11 / 55%	8 / 40%
Apparently quiescent	25	4 / 16%	9 / 36%	10 / 40%	2 / 8%	4 / 16%	2 / 8%	2 / 8%	7 / 28%	9 / 36%	1 / 4%		1 / 8%	5 / 42%	6 / 50%
Slightly active	29		7 / 24%	20 / 69%	2 / 7%		1 / 3%	2 / 7%	9 / 31%	15 / 52%	2 / 7%		1 / 5%	9 / 41%	12 / 54%
Moderately active	20			15 / 75%	5 / 25%				3 / 15%	15 / 75%	2 / 10%		4 / 20%	7 / 35%	9 / 45%
Markedly active	16			8 / 50%	8 / 50%				3 / 19%	9 / 56%	4 / 25%		7 / 44%	3 / 19%	6 / 37%

The change in graph, sedimentation index and sedimentation time indicates a corresponding change in the clinical condition of the patient.
< Less than.

It is not unusual to see patients with far advanced lesions, with cavitation, with marked constitutional symptoms, lose their symptoms or have them materially lessened and clinically appear much improved after a brief stay in the Sanatorium. "Rest in tuberculosis is like giving a patient with active symptoms of acute appendicitis a dose of morphin. You mask all the symptoms but the pathologic activity goes on just the same, and after the morphin loses its effect the manifestations of clinical activity return. Rest, widens the interim between pathologic and clinical activity."[14]

It is in this type of patients that the sedimentation test is most needed and it is here that it should prove of value. During this period of quiescence the physician cannot rely upon temperature or pulse rate, because both are normal. There are no constitutional symptoms to guide him. Physical signs change very slowly and are not a safe criterion. Judgment must be based on clinical experience and caution. Step by step the physician feels his way, prescribing a few minutes exercise at a time, observing closely the reaction of the patient and hoping for the best. This process is continued until the patient reaches that point where he can perform the ordinary requirements of life over a reasonable length of time without a recurrence of constitutional symptoms when he is discharged as an apparent cure. This is the average state of affairs of the average tuberculous patient.

If, therefore, this test is of any value in helping the physician to estimate activity and to replace uncertainty with certainty, it should be welcomed as a valuable addition to the treatment of pulmonary tuberculosis. That the sedimentation test is a delicate measure of pathologic activity is evident from the results shown in our table. But the citing of one or two incidents will not be amiss.

Mr. W. L. is afflicted with chronic tuberculosis of the lungs of long standing and was first admitted to the White Haven Sanatorium in 1920 where he was treated for five months. During this time he showed little constitutional disturbance and did well. The next seven months he worked on the staff and in September, 1921, believed himself sufficiently recovered to assume his old position in a shirt factory. In November, 1925, he returned to the Sanatorium to work on the staff, ostensibly for the purpose of "vacation" and rest. During all this time he was apparently free from symptoms and did not lose weight. On November 6, 1925, I performed a blood sedimentation test and to my surprise the graph was a diagonal curve which meant an active tuberculous process. As this happened in the early part of my study, I could not explain it for here was an individual apparently in good health with normal temperature, and pulse rate with good weight and able to do from six to eight hours of work daily, yet according to the sedimentation test he was harboring an active tuberculous lesion.

On December 2, 1925, he had a moderate-sized hemoptysis (100 cc.). There were no other symptoms. I questioned him closely and obtained the following facts: He did not return to the Sanatorium simply for rest, but because for the past two or three months he felt himself slipping and that during September, 1925, he had a small pulmonary hemorrhage.

Physical examination of his chest revealed medium crackling rales over his left upper lobe, most of his left lower lobe and over the upper half of his right upper lobe. Breath and voice sounds and percussion note were abnormal over the same areas. When these findings were compared with those obtained on previous occasions, no practical difference was noticed. The crackling rales were present on his first admission in 1920 and again in 1923 and were still present on December 3, 1925. This patient was put under rest treatment and in a short time was returned to his position on the staff.

Mrs. R. S. had a far advanced lesion of pulmonary tuberculosis, and her disease had a tendency to progress. On admission August 2, 1925, her temperature was 100° F. (37.8° C.) and her pulse 110. After twelve weeks in bed her temperature and pulse became normal and remained so for four weeks prior to the taking of a sedimentation test; at which time she was allowed out of bed two hours daily with permission to increase this gradually until she was out of bed all day.

The blood sedimentation test taken on November 16, 1925 showed a diagonal curve which meant that this patient was still mildly active in spite of her satisfactory clinical condition. Her temperature and pulse remained normal for about twelve days after the test was taken and the patient was apparently doing well and gaining in weight, when without warning, she had a hemoptysis of about 200 cc. (6 to 7 ounces). Her temperature rose from normal to 100° F. (37.8° C.) and continued between 100° and 102° F. (37.8° to 38.8° C.) thereafter. Her pulse ranged between 100 and 120. Her condition became so serious for a while that her people were sent for. I have since learned that this patient has died.

These cases illustrate several things. In the first place, they indicate that the sedimentation test is a reliable index of pathologic activity and that it will reveal activity before it becomes manifested clinically. In the second place, and as a corollary of the first, the sedimentation test is a more reliable index of activity than temperature, pulse rate or gain in weight—the three major guides in the treatment of tuberculosis. Both patients had normal temperature and pulse rate with a satisfactory weight, yet both were active as was proved by later developments. This activity was not manifested clinically until sometime after it was revealed by the sedimentation test. The physical signs were of no help in deciding either for or against activity.

In the groups classed as "apparently disease arrested," "disease arrested" and "apparently cured" the test yields large percentages of normal findings, and the better the cure, the larger the percentage. This is in marked contrast to that observed in the clinically active groups, where all findings, without exception, were abnormal.

From this observation it would seem that whatever inconsistency there is between the test and the clinical classification must be referred to the classification and not to the test. The classification is a purely arbitrary thing, and must share the burden of proof.

Summary of Results. In healthy individuals and in tuberculous individuals in whom the disease has become absolutely quiescent, the graph is normal, that is, it is a horizontal line.

In tuberculous individuals in whom the disease is not absolutely quiescent but who do not have sufficient pathologic activity to develop constitutional symptoms, the graph is usually a diagonal line but with a variable sedimentation index which is directly proportional to the degree of pathologic activity.

In tuberculous individuals in whom the patholgic activity is such that constitutional symptoms develop, the graph obtained is usually a diagonal or a vertical curve, but with a variable sedimentation time which is inversely proportional to the severity of the infection.

Diagonal curves are obtained chiefly in clinically slightly to moderately active tuberculosis, while vertical curves are obtained chiefly in clinically moderately to markedly active tuberculosis.

There is one important exception to what has been said. Sometimes, it will be seen that although the patient is obviously getting worse and about to die, the graph will change from vertical to diagonal curve, or even to diagonal line of small index, apparently the phenomenon responsible for the sedimentation reaction disappears in some cases shortly before death.

Comparative Values of Sedimentation Test and Symptoms. That the blood sedimentation test is a more reliable index of the presence or absence of activity than the temperature, pulse rate, gain in weight or physical signs, has already been mentioned.

No definite relation was found between the sedimentation test and the following: (1) Extent of pulmonary involvement; all patients were classified according to the Turban system into Stages I, II, and III, but no definite relationship could be established between the extent of involvement and the sedimentation test. (2) Curved nails and clubbed fingers. (3) Duration of disease. (4) Duration of clinical activity. (5) Presence or absence of tubercule bacilli in the sputum. (6) Cough and expectoration. (7) Statement of the patient as to his general condition.

It is evident therefore that in estimating activity the blood sedimentation test is more trustworthy than any one of the symptoms and signs enumerated.

Conclusions. 1. As an aid in estimating activity, the sedimentation test is more reliable than temperature curve, pulse rate or gain in weight, the three major guides in the treatment of tuberculosis.

2. By repeating the test at regular intervals, the true course of the disease can be graphically represented, for as the individual improves the graph should approach more and more the horizontal line, but should he become worse, more and more the vertical curve.

3. Enough clinical evidence has been published by various individuals using diverse technique to warrant the adoption of this test as a routine procedure in institutions responsible for the care of tuberculous patients.

4. The sedimentation test is a nonspecific reaction, occurring in many infectious and destructive diseases and should be studied extensively so that its limitations and probable value could be fully established.

5. The graphic method is the most informative method that has yet been proposed for the study of the blood sedimentation test and should be the method of choice in all future investigations.

NOTE.—I wish to express my thanks to all those who have helped me with this work and especially to Miss A. Steves, Mr. L. F. Treguboff, Dr. L. Jonas, Dr. Joseph Walsh, Dr. Elmer H. Funk and Dr. Lawrence F. Flick. The service of the American Medical Association and of W. F. Prior Company, Inc., in supplying me with literature was of great help.

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14. Discussion by Dr. Allen J. Hruby, on article by Brown (2) p. 102.

REVIEWS.

INTESTINAL TUBERCULOSIS. ITS IMPORTANCE, DIAGNOSIS AND TREATMENT. A STUDY OF THE SECONDARY ULCERATIVE TYPE. By LAWRASON BROWN, M.D., Chairman of the Medical Board of Trudeau Sanatorium, and HOMER L. SAMPSON, Roentgenographer of the Trudeau Sanatorium. Pp. 304; 112 illustrations. Philadelphia and New York: Lea & Febiger, 1926. Price, $4.00.

THE monograph is written by a clinician and a roentgenologist who have made noteworthy contributions to the subject with which it deals. The book is strictly limited to a discussion of intestinal tuberculosis secondary to tuberculosis of the lungs and observations of the writers are combined with full consideration of the literature of the subject. Having in mind the aphorism of Hippocrates, "Diarrhea attacking a person with phthisis is a mortal symptom," the authors have shown that intestinal tuberculosis is not infrequently recognizable by Roentgen ray examinations early in the course of pulmonary tuberculosis. Furthermore they show that control of the intestinal complication may be essential to success in control of the pulmonary disease.

E. O.

ESSAYS IN PSYCHOPATHOLOGY. By WILLIAM A. WHITE, M.D. Pp. 140. New York and Washington: Nervous and Mental Disease Publishing Company, 1925. Price, $2.50.

THE essay on "Primitive Mentality and Racial Unconscious" contains an original and interesting presentation on the regions of consciousness. A diagram is made of a triangle with its base down. In the apex of this triangle is the field of awareness. In the space just beneath is the foreconscious zone where materials of all sorts that are immediately available are stored. Next comes the region of personal unconsciousness, the unconsciousness of the Freudians, which is the much famed psychoanalytic area and where is stored matter that, before being repressed or shoved back, occupied the conscious field. Then follows the intrauterine area and finally the racial unconscious territory.

The writer is conspicuously synthetic in his efforts and, though

the constructive worker is always a favorite target for men of meaner minds, this foremost Freudian is perhaps overzealous when he states that "Freud's contributions may very properly be considered of as great importance to psychopathology as Darwin's was to biology." N. Y.

EXPERIMENTAL INVESTIGATIONS INTO THE EMOTIONAL LIFE OF THE CHILD. By HELGA ENG. Translated. Pp. 243, with 9 plates. Oxford University Press, 1925. Price, $6.50.

A PAINSTAKING study from the Psychological and Physiological Institutes of the University of Christiania. The problem was to determine how far different psychical processes were accompanied by definite changes in the volume pulse curve and the respiration through the use of the plethysmograph and the pneumograph.

The process of attention caused falling volume curve, decrease in pulse height, retarded pulse, retarded respiration. Psychical work gave a rising volume curve, increase in pulse height, accelerated pulse, accelerated respiration.

Spontaneous pleasure emotions caused rise in volume curve, increase in pulse height, retarded pulse and accelerated respiration.

Depression is indicated by a low even volume curve, a very low and weak pulse, retarded pulse and retarded respiration.

The theory of James and Lange that the organic changes constitute the emotion is not in accord with the observations of the author.

The hypothesis of Thalbitzer, that there is a particular emotion center in the brain, is to some extent deemed probable, and it is assumed that such a portion of the brain is in close relationship to the respiratory and vasomotor centers. N. Y.

PEDIATRICS OF THE PAST. An Anthology Compiled and Edited by JOHN RUHRÄH, M.D., Professor of Diseases of Children, University of Maryland, with a foreword by FIELDING H. GARRISON, M.D. Pp. 592; 54 illustrations and 18 full-page plates. New York: Paul B. Hoeber, Inc., 1925. Price, $10.00.

IN a characteristically entertaining foreword Garrison explains, *inter alia*, the difference between the anthology, the chrestomathy and the source book, and points out that the present collection is a combination of the three. Of the forty-five selections, ranging from Hippocrates to Meissner, some comprise mainly of selections from the best work of the author, others present "specimen extracts from the literature of a foreign language," while still others give

the basic, original texts. Three of the earlier pediatric tracts (of Thomas Phaer, Felix Wurtz and William Heberden) are given in full. Each selection is accompanied by evaluating or interpretative remarks which add so greatly to the interest of the original documents, that we must be grateful to the author for his "sort of personally conducted tour," even though this easy access may rob more enthusiastic searchers of some of the joys of discovery. To those thus inclined the two bibliographies at the end of the volume will perhaps offer sufficient opportunity. The compiler's rambling style and unwillingness to confine himself strictly to pediatrics are far from unpleasant features in a work of this kind, which is obviously, as he states in his preface, "a labor of love." Hoeber is again to be congratulated on producing a praiseworthy achievement in a fitting manner. E. K.

CLINICAL RESEARCHES IN ACUTE ABDOMINAL DISEASE. By ZACHARY COPE, B.A., M.D., M.S. (LOND.), F.R.C.S. (ENG.). Pp. 148; 31 illustrations. New York: Oxford University Press, American Branch, 1925.

THIS little book brings out many points in diagnosis and differential diagnosis to which little attention has been paid in the larger textbooks. The older surgeons and physicians use to have what to us seemed an uncanny insight into human ills and a power of diagnosis which seemed beyond us. When this power is analyzed it simply means that constant observation and experience through years of practice has led them to watch the sign posts, so to speak. The author pays particular attention to this feature of diagnosis, and contributes to the reader some very excellent information.

The book is a useful one both for undergraduates and practitioners. E. E.

REPORTS OF THE ST. ANDREW INSTITUTE FOR CLINICAL RESEARCH. Volume II. Pp. 190; 31 illustrations. London: Oxford University Press, 1924.

ELEVEN articles by Sir James Mackenzie, Walker, Orr, Herring, Waterson and Paton on the various topics being investigated by this admirable institute. (See Review of Volume I, *American Journal of the Medical Sciences*, 1923, **165**, 596.) E. K.

BOOKS RECEIVED

CHININUM. Pp. 262; 32 illustrations. Amsterdam, Holland: Bureau for Increasing the Use of Quinine, 1926.

AN INTRODUCTION TO THE STUDY OF *X*-RAYS AND RADIUM. By HECTOR A. COLWELL, M.B., D.P.H., and CECIL P. G. WAKELEY, F.R.C.S. (ENG.). Pp. 203; 37 illustrations. New York: Oxford University Press, American Branch, 1926. Price, $3.35.

A TEXTBOOK OF MIDWIFERY. By KEDARNATH DAS, C.I.E., M.D. Pp. 495; 281 illustrations. Calcutta, India: Thacker, Spink & Co., 1926.

THE BACTERIOPHAGE AND ITS BEHAVIOR. By F. D'HERELLE. Translated by GEORGE H. SMITH. Pp. 629; 25 illustrations. Baltimore: Williams & Wilkins Co., 1926. Price, $8.00.

DISEASES OF THE NEW BORN. By JOHN A. FOOTE, M.D. Pp. 231; 85 illustrations. Philadelphia: J. B. Lippincott Company, 1926. Price, $5.00.

NEURITIS AND NEURALGIA. By WILFRED HARRIS, M.D. (CANTAB.), F.R.C.P. (LOND.). Pp. 418; 45 illustrations. New York: Oxford University Press, American Branch, 1926. Price, $4.00.

HANDBOOK OF DISEASES OF THE RECTUM. By LOUIS J. HIRSCHMAN, M.D., F.A.C.S. Fourth edition. Pp. 403; 257 illustrations. St. Louis: C. V. Mosby Company, 1926. Price, $6.50.

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THE PRIVATE PRACTITIONER AS PIONEER IN PREVENTIVE MEDICINE. By SIR GEORGE NEWMAN, K.C.B., M.D., D.C.L. Pp. 47. New York: Oxford University Press, American Branch, 1926 Price, $0.30.

MODERN METHODS OF AMPUTATION. By THOMAS G. ORR, A.B., M.D., F.A.C.S. Pp. 117; 125 illustrations. St. Louis: C. V. Mosby Company, 1926. Price, $3.50.

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MATERIA MEDICA AND THERAPEUTICS. A TEXTBOOK FOR NURSES. By LINETTE A. PARKER, B.Sc., R.N. Pp. 364; 35 illustrations. Philadelphia: Lea & Febiger, 1926. Price, $2.50.

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The Diagnosis of Clinical Hilum Tuberculosis.—In a very brief, somewhat destructive paper, but one pregnant with good common sense, HAWES (*Boston Med. and Surg J.*, 1926, **194**, 91) discusses the diagnosis of this usually occult form of tuberculosis. He says that for a positive diagnosis the history of exposure, real malnutrition and real underweight, ease of tire (being tired all the time) and temperamental changes are important for a positive diagnosis. Of importance, but not essential to a diagnosis are a positive von Pirquet and Roentgen ray evidence of marked hilum changes. For a negative diagnosis he considers of value the presence of tonsils, adenoids, etc., that can account for symptoms; apparent but no real underweight; negative von Pirquet repeated in the absence of factors that would tend to make is negative; the absence of ease of tire and fatigue. Of value, but not essential in making a diagnosis is negative Roentgen ray evidence.

Fallacies of the "Yeast Method" of Detecting Glucose in the Urine: Further Observations on a Mycologic Method to Identify Various Sugars and Other Carbon Compounds.—For many years we have been taught that the dropping of a small piece of yeast into a fermentation tube containing urine in which sugar is supposed to be present is a specific method by which we can determine the presence of glucose. CASTELLANI and TAYLOR (*J. Am. Med. Assn.*, 1926, **86**, 523) call attention to the fact, and show by their experimental studies that this test is not specific for glucose. The ordinary bakers' yeast not only fer-

ments glucose, but also galactose, maltose, levulose and many other sugars. In order to determine positively what type of sugar it is which is fermented by the yeast, the former author has recommended a mycologic method. To carry this method out it is necessary to have various types of monilia which ferment different types of sugar. For the identification of glucose Monilia balcanica is probably the best of the yeasts. The next best organism is Monilia krusei, which ferments either glucose or levulose or both and no other sugars. This method of the former author is extremely simple and requires only ordinary fermentation tubes plus the cultures of the various types of monilia. In a period of four days the fermentation tubes can be studied, and it can be determined what type of sugar has been responsible for the fermentation in the tube.

Can Insulin Produce even a Partial Cure in Human Diabetes Mellitus?—One of the interesting phases of the use of insulin is the question of whether it is possible to produce a cure of the disease, diabetes, with this specific hormone. The question has been studied in various places and by various men, and at the present time there is considerable divergence of opinion as to this possibility. HARRISON (*Quart. J. Med.*, 1926, **19**, 113) has attempted to answer this question in a very careful study of 5 selected cases of diabetes. He has attempted to obtain indirect evidence which may be interpreted for or against the possibility of the formation of fresh islet cells. As a result of a study of these cases, the periods of time lasting from eleven to eighteen months, he could find no evidence of even a partial remission of the disease, and he found that all patients needed as much or slightly more insulin at the end of the observations as they needed at the start. These 5 patients with diabetes have been followed very carefully. No criticism can be made of the very careful clinical observations. It does seem, however, that the author does not accord with most observers who have used insulin. Of course, in total diabetics in whom there is no islet tissue it is impossible to conceive of regeneration of these cells so as to add the exogenous insulin. It does seem, however, that there are a large group of cases in which there remains a certain limited amount of islet tissue in which the ratio of insulin can gradually be reduced so that eventually it is possible to stop insulin entirely. In these cases it is possible that there is a functional exhaustion and part of the cells at least, after the prolonged rest as a result of insulin therapy, are able to renew their functional activity with sufficient increase of insulin to do away with the necessity of adding insulin from animals.

The Origin of the Lepra Cell.—Virchow first noted in leprous lesions a large number of large phagocytic cells crammed with bacilli, to which he gave the name of "lepra cells." These cells are presumably pathognomonic of leprosy, and they make up the largest portion of the leprous nodule. Their morphology is constant, but their origin is not known. J. OLIVER (*J. Exper. Med.*, 1926, **43**, 233), by means of vital staining, has found that the leprous cell in rat leprosy arises from the histiocyte and is apparently similar to the origin of epithelioid cells of tuberculosis.

SURGERY

UNDER THE CHARGE OF

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Urinary Antisepsis—The Clinical Application of Experimental Data.—DAVIS (*Minn. Med.*, 1926, **9**, 151) states that there is no known "cure-all" for infections of the urinary tract. In other words the ideal internal urinary antiseptic of proven clinical efficiency does not exist. Certain drugs with laboratory findings such as to indicate a theoretical clinical value and which will cause the secretion of the antiseptic urine by normal individuals are clormercury, fluoroscein, acriflavin, mercurochrome and hexylresorcinol. Acriflavin is of distinct clinical value in acute urinary infections. It gives results in chronic infections which are inconstant and not permanent. Furthermore, chemically pure acriflavin is obtained with difficulty and gastrointestinal symptoms are not infrequent. Mercurochrome seems to have given good results in some cases. It is, however, not dependable. Moreover, there are severe reactions associated with the intravenous administration of mercurochrome. It is excreted in the urine only in a small percentage. Mercurochrome is of definite and proven value in the form of local instillations into the bladder or posterior urethra. Hexylresoricinol is of splendid experimental promise, but awaits clinical confirmation. Promiscuous medication with socalled urinary antiseptics without painstaking investigation to eliminate mechanical or systemic causes of infection is distinctly contraindicated. In this field of endeavor there is cause for optimism for the reason that the one greatest obstacle has been surpassed. It has been conclusively demonstrated and confirmed by different observers that there are several chemical compounds which may be passed through the gastrointestinal tract, the blood stream and the kidney of normal human individuals rendering the urine an unfit culture medium for microörganisms and in no way injuring the body. It has been shown that in selected cases one or another of these drugs may exact a curative effect upon inflammatory processes in the urinary tract. In this respect there has been a step of progress made.

Tuberculosis of Glands in the Ileocecal Angle: A Cause of Pain in the Right Iliac Fossa.—BRAITHWAITE (*Brit. J. Surg.*, 1926, **13**, 439) says that it is probably time that old tuberculous disease of abdominal lymphatic glands is very commonly found in the process of operations done for other abdominal conditions. A correct diagnosis was not always made. Some cases with a relatively short history, were not discriminated from subacute appendicitis. In others, the mimicry

of malignant disease was so perfect that the doubt was only solved on histologic examinations of the specimen after operation. Not infrequently the processes cause severe attacks of an inflammatory nature accompanied by abdominal tension, at other times again symptoms appear which remind one of ileus. These misleading symptoms accompanied by the periadenitis signs are to be attributed to intestinal spasms. Radioscopy is essential and a correct diagnosis is easy if differential factors are clearly worked out. Calcified glands are multiple, irregular and mottled in appearance. Their relative positions can be altered. Clear differentiation from renal and ureteral calculi are given by the author. Phleboliths and the teeth or bone of dermoid cysts are usually well down in the pelvis and need hardly be considered in the differential diagnosis. In the factor of macroscopic varieties, there is the stage of infection, analogous to simple adenitis, which subsequently becomes tuberculous, second, the stage of spotted caseation, third, the stage of spotted calcification, fourth, a stage of massive caseation and finally a defensive stage of massive calcification. Conservative measures in treatment are emphasized by the author. Wide excision of the cecum with a portion of the small intestine has never been called for in the author's experience. As in tuberculous peritonitis, opening of the abdomen alone seems to exert a beneficial effect whether as a result of the congestion of the abdominal cavity, and particularly of the portion handled, or as a result of the filling of the abdominal cavity with air or in acute cases of a short temporary paralysis of the ileum and cecum and the temporary fixation of the abdominal walls. Whatever local treatment is adopted, it should be followed by heliotherapy. By heliotherapy is understood treatment not only embracing exposure of the whole body to sunlight and clean air, but also the ingestion of plenty of wholesome food.

The Treatment of Intraoral Carcinoma by Contact Application of Radium.—GRIER (*Am. J. Roentgenol. and Rad. Ther.*, 1926, **15**, 201) believes that epitheliomas inside the mouth differ from those of the face in these particulars: they grow rapidly and involve underlying structures early. Metastasis occurs earlier, while resistance to radiation is more pronounced. Moreover the growths are kept constantly moist by infected fluids while light and air are excluded. These conditions promote infection and hinder the repair of the ulcer left after destruction of the lesion by irradiation. Surgery, however, is seldom seriously considered in extensive intraoral malignancy. The actual cautery is better, but leaves much to be desired. Electrocoagulation in the hands of a few has given very good results, but usually must be supplemented by radium. In outlining a plan of treatment for any case of cancer of the mouth, two facts should be kept constantly in mind. The first is that of metastasis to the lymph nodes, the most serious complication which can occur and the second is that traumatism to the primary lesion may promote metastasis. In order to combat cervical metastasis the neck should either be thoroughly irradiated before treatment of the primary lesion or if the individual preference is for a block dissection of the neck, that may be done. The technique is described in detail. The two chief advantages of this method of treatment are the absence of sloughing and less danger of exciting metastasis. A radium reaction follows the

treatment but this is superficial and is not nearly so painful as a slough, and heals readily. It comes on about ten days after treatment and is active for about ten days more. On the other hand, introduction of radium needles or emanation seeds is always accompanied by a certain risk of sloughing either from the necrosis which occurs around the needles, or from infection incident to their insertion.

PEDIATRICS

UNDER THE CHARGE OF

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The Role of Dentition in the Diagnosis of Rickets.—BLUM and MELLION (*J. Am. Med. Assn.*, 1926, **86**, 677) included in their study a large number of babies, beginning several years ago when cod-liver oil was not used as a therapeutic agent. This study extends to the present time when the drug is used in a routine way. Orange juice was given at all times so that the possibility of scurvy as a factor in delayed teething could be absolutely excluded. These children were examined regularly at monthly intervals and data of the clinical signs of rickets, Roentgen rays of the epiphyses and inorganic phosphorus determinations of the blood were recorded. Although several hundred infants were studied in this manner, only those who had no teeth at the time of the first examination were included in this survey. The time of eruption of the first tooth was observed in 68 infants who had no rickets and 87 who had rickets of various degrees. The diagnosis was substantiated by beading of the ribs, enlargement of the epiphyses, typical Roentgen ray changes and diminished inorganic phosphorus content of the blood. By the manner in which this study was controlled, it was possible to be certain in regard to the diagnosis of the various cases and also to include the important group of mild rickets which would have otherwise been open to question. Only slightly more than 10 per cent of the normal babies had a tooth at six months. The first tooth in the group of infants with rickets did not appear until the seventh month, and even then was noted in only about 1 per cent. Thirty-five, or about one-half of the normal group, had a first tooth during the period from the sixth to the ninth month, but only 23, or about one-quarter of the rachitic infants, had a tooth during this period. Forty-two babies having rickets, or about one-half the total number, gave no evidence of teething before the period of nine to twelve months. At the end of the first year of life all but 1 of the normal babies had a tooth, but only 65, or about 75 per cent, of the rachitic babies had a tooth. Teething was delayed until the twelfth to the fifteenth month in 18 of the babies having rickets, and until the fifteenth to the twenty-first month in 4 cases. It was found that mild rickets as evidenced by clinical Roentgen ray and chemical study showed a delay in dentition

but as a diagnostic sign to rickets delayed dentition is of little significance, as there is a marked variability in the time of the eruption of the deciduous teeth in even apparently normal babies.

Diagnostic Value of Cerebrospinal Sugar Fluid Content.—STOWE (*J. Lab. and Clin. Med.*, 1926, **11**, 307) places the sugar content of the normal cerebrospinal fluid in the neighborhood of 75 mg. per 100 cc. in cases of neurosyphilis and lethargic encephalitis and other neurologic and nonneurologic conditions, other than the forms of meningitis. The deviation from the normal range and middle point is so slight as to be without any diagnostic significance. Tuberculous meningitis gives values so definitely above those of purulent meningitis cases and so definitely below other conditions that an almost certain diagnosis can be made in this disease. The occasional purulent fluids obtained after intraspinous therapy, in brain tumor cases with necrosis or hemorrhage near the ventricles and in sympathetic aseptic meningitis can be rapidly outlined by their normal sugar content over infective meningitis in which the etiological organism may not be found promptly. The presence of pus cells alone in the cerebrospinal fluid does not reduce its sugar content. Two of the cases of this series were interesting in that obstruction to the flow of cerebrospinal fluid at the base of the brain in the one and at the lower dorsal spinal level in the other did not produce any essential difference in the sugar content above and below the lesion. This would suggest that the diffusion of sugar into the cerebrospinal fluid occurs through the cerebrospinal axis rather uniformly and not through the choroid plexis alone.

The Significance of the Blood Chemical Changes in Pertussis.—REGAN and TOLSTOUHOV (*J. Am. Med. Assn.*, 1926, **86**, 1116) report the result of their observations after 682 blood chemistry analyses in cases of whooping cough. They found a diminution of the total inorganic phosphorus associated with the lowering of the hydrogen-ion concentration of the blood, while the plasma bicarbonate remains within normal limits. These changes occur early in the disease, appearing in the case of the inorganic phosphorus in the catarrhal stage. Both alterations are well developed, especially the change in phosphorus, during the first few weeks of the paroxysms and show a certain degree of parallelism in their course which signifies a close interrelation. In moderate and severe cases treated with alkalies the inorganic phosphorus rose steadily from the third week, while in untreated cases of the mild type, the rise did not begin until the sixth week. The same is true in the less decided way of hydrogen-ion concentration value before as compared to this during and after treatment. The diminution of inorganic phosphorus bears no relation to age but only to the stage of the disease and there seems to be no underlying rachitic basis. The calcium content, while exhibiting slight mobility as a result of shifting of calcium in connection with the characteristic phosphorus and hydrogen-ion alterations, has no constant alterations of a distinct type. These changes indicate an acidosis of the uncompensated type which has as a cause the accumulation or increased concentration of free carbon dioxide in the blood. This laboratory observation is easily correlated with several of the symptoms so prominent in pertussis such as the paroxysms of

vomiting, parenchymatous emphysema and convulsions. The vomiting of the disease may be a compensatory mechanism adapted by the body to eliminate acid in an attempt to maintain a normal acid base balance. This contention of the uncompensated acidosis seems further substantiated by the effects on the disease of alkali therapy. Alkalies administered early appear usually to abort the disease and associated with the cure is a rapid rise of inorganic phosphorus and a change in the hydrogen-ion concentration of the blood, while if given late, cure is produced in a relatively short period.

OBSTETRICS

UNDER THE CHARGE OF

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The Use of Low Cervical Operations for Cesarean Section.—Although CONN (*Canadian Med. Assn. J.*, 1926, **16**, 32) has only used this operation a few times, he is much pleased with the result, and believes that there is a very definite place for it in obstetric practice. He believes that the convalescence after operation is smoother, gas pains and distention are not frequently present and the danger of rupture at subsequent pregnancies is less.

The Use of Fluids in the Treatment of Hyperemesis Gravidarium.—In the opinion of HARDING and VAN WYCK (*Am. J. Obst. and Gynec.*, 1926, **11**, 1) there is a misinterpretation of data in the two recently published papers advising the use of sodium bromid and the other advocating the use of insulin together with glucose in the treatment of hyperemesis. They consider the most important factor that of dehydration. They believe that dehydration is so important that any patient admitted for vomiting of pregnancy to the Toronto General Hospital is at once treated, as a matter of routine, with 1000 cc. of 5 per cent glucose solution and 1 per cent saline given intravenously each day until a diuresis is obtained or until the twenty-four-hour output of urine shall reach at least 1000 cc. and shall have a specific gravity of 1010 or less. At the same time rectal enemata of 200 cc. of 10 per cent glucose in normal saline are given three times daily and at bedtime 30 to 60 gr. of sodium bromid are given in each enema for the first day or so. Patients are encouraged to drink any liquid they may fancy except tea, coffee, milk or cocoa. The treatment may thus briefly be described as rest in bed, with isolation, during the forcing of fluids by all routes. They have found that their recent records show, in uncomplicated cases, patients able to take small meals from three

to six days. The average for 14 cases was four and one-tenth days, from admission to cessation of vomiting and the taking of food. Their conclusions are that the successful treatment of hyperemesis gravidarium depends on the use of fluids.

Elimination of the Second Stage of Labor in Breech Presentations.—Irving and Goethals (*Am. J. Obst. and Gynec.*, 1926, **10**, 80) have been assigned to handle all breech cases at the Boston Lying-In Hospital for the period of a year. As a summary of the records showed a mortality of 9.78 per cent in the last ten years, their figures show that breech delivery entails a higher fetal mortality than any other type save the operation of high forceps, and they have, during the past year, carried out the following routine method of procedure: (1) Careful ausculation of the fetal heart throughout labor; (2) the policy of hands off during the first stage except when, because of lack of progress after rupture of the membranes prematurely, a Voorhees bag is inserted to aid dilatation or stimulate uterine contractions; (3) immediate extraction after full dilatation. A series of 30 cases gave them a fetal mortality of 2. This method is to be continued over a period of time.

The Antagonistic Functions of the Uterus in Relation to Regional Nerve Blocking.—Cooke (*California and West. Med.*, 1926, **24**, 55) says the fundus uteri and upper uterine segment functioning to contract in labor, are under the control of the involuntary nerves of the sympathetic system with the assistance of their own intrinsic nerve centers in the uterine muscle. The lower uterine segment, cervix, vagina, muscles of the floor of the pelvis, the vulva and the perineum comprise the birth canal and are innervated from the cerebrospinal system with motor and sensory function. The etiology of childbirth pain is not due to the involuntary contractions of the upper segment, but is in the stretching and trauma of the entire birth canal through which the child must pass. Spinal anesthesia and regional nerve blocking inhibit these motor and sensory impulses from the birth canal (H. T. Cooke: Technique: Spinal Analgesia in Obstetrics, including Cesarean Section, *American Journal of Surgery*, October, 1925), and allow a "painless conscious childbirth." The author believes this result is attainable not only for operative obstetric procedure but for the average woman.

Cesarean Section for Hemorrhage.—Smith (*California and West. Med.*, 1926, **24**, 39) states that in only a small percentage of cases of placenta previa, approximately 5 per cent, is Cesarean section indicated, and these include cases with a long rigid os, viable child, pelvic distortions, cardiac disease or cases that have other complications in addition to placenta previa. On the other hand, Cesarean section should be the method of choice in the treatment and should be promptly done in almost all cases of accidental hemorrhage. His records show 28 cases of placenta previa and 12 cases of accidental hemorrhage in a total of 4002 cases. Published statistics do not show improvement in the mortality rate of mothers from operation for placenta previa but do show marked increase in the chances of survival of the child. In accidental hemorrhage there is a marked improvement in the maternal mortality but no change in fetal mortality.

GYNECOLOGY

UNDER THE CHARGE OF
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Paroxysmal Tachycardia following the Rubin Test.—The use of Rubin's method for the determination of tubal patency has become so general because of its great value, and also on account of the comparative ease of its execution, that it appears advisable that we should call attention to a complication which has been reported by KERN (*J. Am. Med. Assn.*, 1926, **86**, 623). In the case he reports the patient who was in obvious health before the test was performed and who left the physician's office in apparently good condition, returned about an hour later with considerable pain in the chest and side of the neck. The pain was very intense and was made much worse by breathing and was complicated by a marked cardiac palpitation, the rate of the heart being 152 beats per minute. When the patient was placed in a recumbent position all of the symptoms disappeared and the pulse rate dropped to normal. However, on assuming the sitting position again the symptoms returned but in a milder degree which were again relieved by assuming the recumbent position. Kern calls attention to the fact that he believes all of these symptoms were due to the collection of air under the diaphragm when the patient assumed the sitting position, and he cautions against the use of air in performing this test because of its slow absorption and advises that carbon dioxid should be used routinely as originally recommended by Rubin, since any symptoms which would occur from the presence of carbon dioxid would rapidly disappear because of its quick absorption.

Treatment of Endocervicitis with Strong Mercurochrome Solution.—In his work in cases of gonorrheal endocervicitis, BRADY (*Bulletin of the Johns Hopkins Hospital*, 1925, **37**, 400) has used a 20 per cent solution of mercurochrome and his experience has shown that, for the endocervix, this drug is absolutely safe in this strength. There has never been any evidence of general toxic symptoms developing nor of any local destruction of tissue. He has painted a series of normal cervices with iodin, another with 10 per cent silver nitrate and a third series with 20 per cent mercurochrome and two days later reëxamined all these patients. Less local reaction followed the use of the mercurochrome than after the other two drugs. Pure carbolic acid, of course, causes much more local destruction of tissue than any of these drugs. Briefly, the method of treatment has been as follows: The patient received douches daily except during the menstrual periods and on the day on which smears were to be taken. Twice a week she was placed in the lithotomy position and the cervix well exposed with a bivalve

duckbill speculum. The amount of discharge coming from the external os was recorded and the discharge then carefully removed. The entire vaginal portion of the cervix was well painted with 20 per cent mercurochrome and then a small amount of cotton on a thin wire applicator well soaked in this solution was introduced into the external os and carried through the cervical canal to the internal os. Occasionally, the applicator would slide so easily through the cervix that it would impinge on the fundus uteri. There has been no instance in the series in which the patient, after the entire treatment has been carried out with mercurochrome and three negative smears obtained at two-week intervals, has returned with positive smears at the end of a month without treatment. In the 24 cases for which an absolute cure is claimed, the average time the patient was under his care, including the month in which all cervical treatments were suspended, was three and two-third months. Grouping together the 24 cases of absolute cure and the 5 cases of probable cure, in these 29 cases in 14 instances the smear taken at the end of two weeks' therapy was negative and gonococci were never found in the discharge after that time. In 7 other instances the third smear taken, that is, the one after one month's treatment, was negative and no further positive smear was obtained. Four patients gave a negative smear at the end of two months and three others at the end of ten weeks. One patient required four months to cure.

Value of the Sedimentation Test in Pelvic Disease.—During the past few years we have presented several reports on the blood sedimentation test which were rather enthusiastic as to its value in the diagnosis and prognosis of disease in the female pelvic organs. The chief claim of its proponents has been that it was a specific test in the determination of the virulence of the invading bacteria and as an indicator of the time of safe surgical intervention, also being of aid in the differential diagnosis of inflammatory from noninflammatory tumors. This subject has been investigated by SCHMITZ and SCHMITZ (*Am. J. Obst. and Gynec.*, 1926, **11**, 353) who give a report of their findings. They state that the determination of the sedimentation speed by the sedimentation test shows that of 46 infections 37 were acute and subacute, and 29 of these had a sedimentation time of sixty minutes or less; while in 8 cases the sedimentation time was well above sixty minutes. The average sedimentation time in normal adults was about three hundred and sixty minutes; in the infectious cases about eighty minutes; in the patients with myomata about sixty minutes; and in the patients with carcinomata about forty minutes. The prognostic and diagnostic aspects of the sedimentation test were ascertained first, by determining the time of safe operability by the usual customary methods, that is, blood analysis and temperature; and second, by taking the sedimentation speed on admission and before operation. A comparison of the results shows that 17 patients with infections and 12 patients with myomata were subjected to operation, though they had sedimentation speeds of sixty minutes or less. All had a normal recovery except one patient who developed a pelvic cellulitis, postponing recovery for two weeks. According to Linzenmeier, Friedländer, Baer and Reis and others, patients suffering with adnexal infections and having a sedimentation speed of sixty minutes or less should not be subjected to operation, as

the invading bacteria are still virulent. Morbidity, and even mortality should have resulted from untimely surgical interference. Morbidity, however, was seen in only one instance. Clinical observation and blood analysis are of primary importance in the determination of the time of safe operability in diseases of the female pelvic organs. The sedimentation test cannot supplant them. The differential diagnosis of inflammatory adnexal tumors and myomata, or of myomata and carcinomata cannot be facilitated by the sedimentation test. Twelve out of 14 cases of myomata had a sedimentation time of less than sixty minutes and all the 8 cases of carcinoma had a sedimentation time of less than sixty minutes. The number of benign and malignant growths subjected to the sedimentation test is small, yet the conclusion must be drawn that the test is probably not of diagnostic importance. Clinical training and clinical observation must remain the methods of correct diagnosis. The sedimentation test could not even corroborate such findings.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Local Immunization of Tissues of the Nose, Throat and Ear by Bacterial Vaccines.—Following certain observations of Besredka on local immunization with typhoid vaccines, HAYS (*Arch. Otolaryngol.*, 1925, **2**, 321) applied autogenous vaccines to the parts affected in various diseases of the nose, throat and ear. The vaccines consisted of forty-eight-hour cultures in 1 per cent glucose meat extract or meat infusion broth, which were sterilized by heating in a water bath for one hour at 60° C. Occasionally a salt solution suspension of the sedimented bacteria was employed instead of the broth medium. Identification of the various bacteria showed that streptococci and staphylococci predominated. The vaccines were applied as near to the infected part as possible. In nasal conditions long strips of cotton gauze immersed in the vaccine were introduced into the nares every three or four days for half an hour on eight occasions. In frontal or maxillary sinusitis the vaccines were instilled into the cavities after irrigation. Diseased conditions of the external auditory canal and middle ear were treated by instilling the vaccine into the ear canal. In wound infections direct application of the vaccine was made. The majority of the 200 cases reported consisted of nasal infections, especially infections of the accessory sinuses. It was found that 61 of the 200 cases had been cured by the treatment; 92 had been markedly improved; 10 were unimproved; in 37 the result was questionable. Of the nasal sinus infections, totalling 69, 23 were cured, 38 improved and 8 unimproved. In 16 cases of acute inflammation of the nasal mucosa 12 were cured and 4 improved; whereas in 5 cases of chronic rhinitis 4 were improved

and 1 unimproved; although 6 of 43 cases of subacute rhinitis were cured, 31 were improved and 6 unimproved. Three cases of ozena were markedly improved. Four cases with asthma and an associated ethmoiditis were treated, 1 of which was cured and 3 were improved. Six patients with acute mastoiditis, on whom operation was performed with subsequent slow healing, were cured. In 13 cases of progressive deafness, with vaccine treatment of the Eustachian tube, 10 were improved—results corresponding closely to other methods of treatment. The author concludes that the vaccines seem to act more beneficially in purulent conditions which can be reached directly and that nasal sinus infections seem to respond more readily than other conditions.

Primary Tuberculosis of Tonsils and Adenoids among Chinese.—Primary tuberculosis of the tonsils and adenoids, as noted in many series of tonsillectomies in Europe and the United States, occurs in approximately 5 per cent. Among those manifesting tuberculosis of the cervical lymph nodes the incidence is much higher. In Crowe's series of 3260 tonsillectomies the incidence increased from 4.81 per cent in the entire series to 48.2 per cent in patients with tuberculous cervical lymphadenitis. More important than the knowledge that primary tuberculosis of the tonsils exists, is the problem of its significance as regards bodily welfare. Many investigators have found an etiologic relationship between tuberculous tonsillitis and the drinking of tuberculous milk, basing their conclusions on either the histologic picture of extirpated tonsils or the finding of tubercle bacilli in the tonsillar tissues or crypts. Other workers, notably Aufrecht, and Harlitz, have called attention to the latency of tubercle bacilli in the lymphatic tissue, implying that these microörganisms often pass through the tonsil to the cervical lymph nodes without leaving evidence of injury in the tonsil. Recognizing the importance of this subject in North China, where native children and young adults show a considerable incidence of tuberculous cervical lymphadenitis, although cows' milk is not used as an article of food, KORNS (*China Med. J.*, 1925, **39**, 899) studied a series of tonsils from 91 patients. Each tonsil was bisected vertically, half being subjected to histologic examination and the other half emulsified and injected, subcutaneously, into the groins of healthy guinea pigs. Seventeen of the 91 guinea pigs died within five days of an overwhelming infection, leaving 74 to be observed further for evidences of tuberculosis. In addition, adenoids from 24 were similarly investigated. The microscopic diagnosis was chronic tonsillitis in all 74 cases, chronic adenoiditis in 23 and tuberculosis of the adenoids in 1. The results from inoculation were positive in 2 guinea pigs, 1 of which was the same case showing tuberculous adenoiditis, microscopically. The author concludes that "while this series is small it would indicate a lower incidence of primary tuberculosis of the tonsils than is found in the west; and that the fact that Chinese do not drink cows' milk may be suspected as being responsible for this difference."

RADIOLOGY

UNDER THE CHARGE OF

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Metastasis to the Bones from Carcinoma of the Breast: A Roentgenologic Study.—Among 1985 cases of carcinoma of the breast examined at the Mayo Clinic during the last six years, 67 (3.48 per cent) had metastasis to bones. These are reviewed by MEYERDING, CARMAN and GARVIN (*Radiology*, 1925, **5**, 486). The bones most commonly involved were the pelvis, femur, lumbar spine and ribs, in that order. Amputation had been performed in 46 cases, and in these the average time between operation and the discovery of metastasis was about thirty-one months. The metastatic lesions are commonly of the osteoclastic type, and are characterized roentgenologically by a honeycombed appearance with a marked decrease of density, and mottling in the affected areas. Rarely, if ever, is there a purely osteoplastic type, but occasionally there are mixed types. Roentgenologic simulants include osteoporosis from disuse, multiple myelomas, osteomalacia, sarcoma, osteomyelitis, osteitis fibrosa cystica and Paget's disease. In every case of carcinoma of the breast, and of middle-aged women with or without a definite history of carcinoma of the breast, who complain of "rheumatic" or "sciatic" pain, the possibility of metastasis to bone should be considered.

Clinical and Experimental Cholecystography.—Both the intravenous and oral method of cholecystography have been used by SOSMAN, WHITAKER and EDSON (*Am. J. Roentgenol. and Rad. Ther.*, 1925, **14**, 495). They consider the intravenous administration of sodium tetraiodophenolphthalein a very accurate test for a nonfunctioning or poorly functioning gall bladder. The oral administration is much easier, but gives more frequent reactions, and is not as reliable. Its chief value is in ruling out definitely normal gall bladders and in revealing a certain percentage of opaque calculi. If the shadow of the gall bladder is faint or absent by this method the intravenous method should be used as a check.

Further Development in the Jejunal and Oral Administration of Tetraiodophenolphthalein, Sodium Salt.—STEWART and RYAN (*Am. J. Roentgenol. and Rad. Ther.*, 1925, **14**, 504) have administered this salt directly into the jejunum through the duodenal tube in 40 cases with gratifying results. Some reaction, such as faintness, vomiting and diarrhea, appeared in a number of cases, but lasted only a short time. For oral administration they have for several months been using keratin coated pills with entire satisfaction, although the pills must be

freshly made for each dose. Recently they have tried capsules coated with resins and these seem to give more satisfactory results than the pills, although exit of the capsules from the stomach is sometimes tardy. Besides aiding in the diagnosis of cholecystic disease, the iodin compound intensifies the shadow of the liver, so that enlargement, irregularities and nodulation, especially along the lower border, can be recognized.

Cholecystography: Its Development and Application.—GRAHAM, COLE and COPHER (*Am. J. Roentgenol. and Rad. Ther.*, 1925, **14**, 487) give a summary of their development of cholecystography, the various substances tried and the present status of the method. At this time they prefer the intravenous administration of sodium tetraiodophenolphthalein. When it is properly given reactions are slight and relatively few. They regard it as a sensitive test of the function of the gall bladder. As a method of diagnosis cholecystography has been found correct in 96.25 per cent of 80 patients operated upon.

Roentgen Ray Study in Bronchiectasis.—It is the custom of SINGER and GRAHAM (*Am. J. Roentgenol. and Rad. Ther.*, 1926, **15**, 54) to make Roentgen ray plates in three positions: (1) Anteroposterior, (2) posteroanterior and (3) horizontal anterior or posterior. Careful analysis of Roentgen ray plates taken in various positions, together with the history and physical signs, gives the best method for making a positive diagnosis. In many cases the bronchiectatic areas show themselves as triangular-shaped densities, with the apex at about the hilum, from $\frac{1}{8}$ inch to several inches wide, extending from the hilum to the diaphragm. The density of these shadows varies with the amount of contained secretion.

Radiation Therapy in 801 Cases of Carcinoma of the Breast.—PFAHLER and WIDMANN (*Am. J. Roentgenol. and Rad. Ther.*, 1925, **14**, 550) present tabulated statistics of their experience covering a period of twenty-five years. Only 37 per cent of the cases were surgical, leaving 63 per cent that must either have been abandoned or treated by radiation. Of all cases, early and late, operable and advanced, inoperable and recurrent, 50 per cent were alive three years and 27 per cent alive five years or more. In the postoperative group, without gland involvement, 81 per cent were alive three years and 77 per cent alive five years or more. In the postoperative group with gland involvement, 56 per cent were alive three years and 38 per cent alive five years or more.

Toxic Goiter: Its Treatment by Means of Radium and the Roentgen Rays.—Radium and the Roentgen rays will probably cure from 66 to 75 per cent of cases of toxic goiter, in the opinion of STEVENS (*Radiology*, 1926, **6**, 7). The results are at least equal to those obtained by any other method of treatment. Patients with large tumors, who present symptoms of pressure, should be operated on for quick relief. If normality in all respects is not realized irradiation can be expected to perfect conditions in many instances. Chronic abscesses or foci of infection should be eradicated in each case, no matter what treatment is advised.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Biochemical Character of Certain Bacteria in Association.—It has been known for some time that bacteria in mixed cultures may give rise to biochemical changes which none of the bacteria contained in the mixture can bring about when isolated in pure cultures. CASTELLANI (*Brit. Med. J.*, 1925, ii, 734) has apparently overlooked the work of Sears and Putnam (*Jour. Infect. Dis.*, 1923, **32**, 270), which deals with the same phenomenon rediscovered by him. This author used a number of Gram-negative bacilli in combinations and tested their reactions on various carbohydrates. He found, as did the earlier workers, that if a particular bacterium, capable of fermenting with acid production but no gas the carbohydrate in the test, had mixed with it another bacterium which could not attack this carbohydrate but could form gas from simpler carbohydrates, such as glucose, that the resulting biochemical change was acid and gas. As an example, when a mixture of Bacillus typhosus and Bacillus proteus was added to mannite acid and gas was produced. Bacillus proteus alone did not attack this compound and Bacillus typhosus only produced acid in it. He considered the subject very obscure, which indeed it is, and he did not offer any theory or hypothesis for his results, although he does state that one of the bacteria of the mixture must be capable of producing acid and gas in glucose, and that not every organism with this character will give rise to the phenomenon when added to mannite in the presence of Bacillus typhosus. The author also apparently was not familiar with the reverse phenomenon reported by Smith and Smith (*J. Gen. Physiol.*,1920, **3**, 21).

Transmissible Bacterial Autolysis or Bacteriophage.—BORDET (*Ann. d. l'Inst. Pasteur*, 1925, **39**, 717) is the chief exponent of the theory that bacteriophage is a manifestation of an exaggerated normal function in the metabolism of bacteria. He is definitely opposed to the d'Herelle hypothesis, that the phenomenon results from the intervention of a foreign parasitic virus. He has very carefully reviewed the whole subject and has brought together a large number of important experiments which are opposed to the d'Herelle view. He particularly attacked the interpretation of the results obtained by the method used by d'Herelle and his school in making counts of the number of elements of the active principle, and has shown that the number of plaques developing under this technique is more dependent on the number of susceptible bacteria than on the actual quantity of the bacteriophage in the mixtures. He further stressed the importance of the critical

stage in the growth of bacteria. This is the stage when the bacteria become most susceptible to the action of the active principle, and it is reached at different times by the different species of bacteria as well as by the individuals in any single culture. He also brings together a number of studies which tend to show that there are many variations in single pure cultures, and he believed that the active lytic principle acting on these variations tends to either stabilize the character of the culture or to cause definite varieties to appear. In experimenting with a particular race of Bacillus coli it was found that this organism started the lytic process in a culture of the Shiga bacillus and that this could be carried on in series, although the principle coming from the Bacillus coli does not cause autolysis in cultures of itself. The author's view is that there are two normal physiologic processes occurring in the life of bacteria, one of building up and the other of breaking down. Under normal conditions these two processes are balanced. The pathologic phenomenon (the lysis) occurs when the active principle which sets free the lysin comes in contact with susceptible bacteria. This occurs under various environmental conditions. He definitely does not believe that the active principle originates from the leukocytes or the glands of the intestinal tract, but that these may play a part in changing the environmental conditions. He draws the analogy between the increase in thrombin, which occurs when a little thrombin is added to a stable plasma as well as the activation of the proteolytic ferment of the pancreatic juice, and the increase in the active principle from the bacteria themselves when the process of autolysis is started.

Lysogenic Power, Active or Spontaneous and Lysogenic, Passive or Provoked.—BORDET (*Compt. rend. Soc. de biol.*, 1925, **93**, 1054), in continuing his studies on transmissible bacterial autolysis, has divided the active principle into two classes: (1) The lysogenic power inherent to the species, it being recognized that the susceptibility of a bacterium to a principle implies the capacity to reproduce it. If such cultures are plated out it was found that each individual colony was made up of bacteria having the capacity to reproduce an active principle. Principles of this kind will act on closely related bacteria and these bacteria easily adapt themselves to it. The varieties of principle how certain peculiarities, depending on the particular variety of bacterium from which they have been derived. (2) The lysogenic power which is foreign to the particular bacterial species, the bacterial species being sensitive in this case only reproduces the active principle when it is in contact with it in the culture medium and it is not inherent to the bacteria themselves. On isolation of the bacteria from such a mixture by plating the individual bacilli, growing as colonies, were found to be unable to reproduce the principle, the process not being in this case part of their intimate physiology. This is the passive or provoked lysogenic power. The author pointed out that the findings outlined above are the opposite to what one would expect if the virus theory were true, since he could readily separate by the method of isolation the spontaneous lysogenic power inherent to the species from the lysogenic power induced or passive when both were present in the same mixture.

The Transmissible Bacterial Lysin and its Action on Dead Bacteria.—One of the important characteristics of bacteriophage or the transmissible bacteria lysin is that it requires living bacteria for its reproduction, and it has been presumed as a result of numerous experiments that it does not act on dead organisms. The contribution of TWORT (*Lancet*, 1925, ii, 642), the first man to accurately describe this phenomenon of bacteriophage, has demonstrated that there is actual destruction of dead bacteria in the process of lysis. The presence of living bacteria in the same mixture is, however, necessary. The proof that such destruction does occur was accomplished by using an emulsion of the organism tested, a white micrococcus, which was killed at 60° C. for one hour. This emulsion was mixed with a sterile broth in four tubes. Tube 1 received no addition, Tube 2 was seeded with living microbes, Tube 3 had added a filtered lysin and Tube 4 had both filtered lysin and living bacteria. The emulsion used gave a decided cloud in the broth and in Tube 4 there was a definite clearing of this original turbidity which indicated quite definitely that both living and dead bacteria were autolyzed in the process. The clearing in this tube was not complete, and it was shown that this was, certainly in part, due to the survival of living cocci. The author does not consider that there is definite proof that the transmissible lysis is a virus, and although there are many arguments in support of this view there are also many that may be used against it. In considering the temperature at which lysin is destroyed he indicates that there are many factors which may alter the findings. D'Herelle has laid particular stress on the differences in the thermal resistance in his experiments, designed to show that the phenomenon originally described by the author is not the same as that which he discovered.

HYGIENE AND PUBLIC HEALTH

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A Comparative Study of Rat-flea Data for Several Seaports of the United States.—FOX and SULLIVAN (*Pub. Health Repts.*, 1925, **40**, 1909) note that plague has never occurred on the Atlantic seaboard of the United States, but has prevailed on the Pacific coast and on the Gulf coast, which, of course, differ climatically from the Atlantic coast. They also point out that Robertson has suggested that the absence of plague in the latter region may be due to the effect of cold weather on flea breeding and on flea longevity; they emphasized that for insects to propagate disease they must not only be present, but they must be present in adequate numbers. They review the previous work on the

subject and present new data with reference to New York, Boston and New Orleans. It was found that the Indian rat flea, a known plague carrier, was predominant in the southern city and rare in the cities of the north. The total number of fleas per rat was also much greater in the southern city.

Report on Probable Origin of Typhoid Fever on a Fishing Schooner.—ROBERTSON (*Pub. Health Repts.*, 1925, **40**, 2209) reports the occurrence of 6 cases of typhoid fever on a small vessel which led to an investigation as to the source. This was found to be a "carrier;" the special interest lay in the following facts: (1) Typhoid bacilli were found in the urine thirteen years after typhoid fever; (2) although the carrier was not a food handler, a number of cases apparently got their infection from him; (3) the typhoid bacilli were found only after repeated examinations.

The Results of the Intracutaneous Tuberculin Test in an Ontario Survey of School and Preschool Children.—ELIOT (*Tubercle*, 1925, **7**, 122) made a general health survey of 1392 children of school and preschool in a typical Ontario town and an adjoining rural township. This included intracutaneous tuberculin tests and single Roentgen ray films of the chest. Four hundred and twenty-six children, or 32 per cent, reacted to tuberculin; 14 children, practically 1 per cent, were considered to have active tuberculosis. Thirty-six per cent of town children reacted and 22 per cent of the rural children. Of the total group about 15 per cent reacted at time of entering school, about 25 per cent at seven years, 40 per cent at ten years and 50 per cent at fifteen years of age. Up to the age of ten the incidence of infection is the same for boys as for girls, but in the age group ten to fourteen the incidence rises more rapidly in girls in the town and in boys in the country. From a comparison with other studies it is quite evident that infection is not as great in rural and small-town communities as in the large cities.

Rural and Urban Health: II. A Comparison of Past Diseases in University Students from Rural and Urban Districts.—SHEPARD and DIEHL (*J. Ind. Hyg.*, 1925, **7**, 481) made a study of students from the University of Minnesota in order to try to discover the occurrence of past diseases according to the size of the community from which they came. For the men it was found that students from rural communities are highest in past histories of pleurisy, pneumonia, rheumatism, smallpox and tuberculosis. They are lowest in histories of chickenpox, diphtheria, tonsillitis, typhoid fever and whooping cough. Students from villages of from 50 to 1000 population are highest in histories of appendicitis, chickenpox, influenza, measles, mumps, nervous breakdown, typhoid fever and whooping cough. They are lowest in past history of chorea, pneumonia and tuberculosis. Students from towns of from 1000 to 5000 population are highest in history of scarlet fever, and lowest in history of pleurisy and rheumatism. Students from cities of 5000 to 50,000 population are highest in history of diphtheria and tonsillities and lowest in history of nervous breakdown and scarlet fever. Students from large cities of over 50,000 population are highest in past history of chorea. They are lowest in history of appendicitis,

influenza, measles, mumps, pleurisy and smallpox. The totals of percentages show that male students raised in villages give a history of having had the most diseases, a total of 368.5. Students from small cities come next with a total of 326.4 and those from towns are third with a total of 301.7. Students raised in the country are fourth highest in history of past diseases with a total of 287. Those raised in cities have had the smallest number of past diseases with a total of 279.1.

Family History in Relation to Prognosis of Pulmonary Tuberculosis.—FORD (*Tubercle*, 1925, **7**, 117) undertook an investigation of the history of over 1000 cases of pulmonary tuberculosis in order to ascertain if the family history had any relation to the prognosis of the disease. Of the 1062 cases 5.18 per cent had a direct maternal history of tuberculosis, 6.87 had a direct paternal history, 7.44 per cent had an indirect maternal and paternal history, 1.03 per cent had direct maternal and paternal history, but 79.47 per cent had no family history of tuberculosis. It also appears that those cases whose mother suffered from tuberculosis seem to do much better than the others. It is interesting to find that the figures so closely agree with Drolet's finding—"children of tuberculous parents do not inherit even a predisposition to the disease but an increasing degree of immunity to it instead." From the figures in this study it would appear that it is the maternal history that is the more important, that if the mother suffers from tuberculosis she is capable of conferring some immunity—either passive or active—on her offspring, with the result that the children are rather less likely to develop active tuberculosis than those with no maternal history. On the other hand, if the children do develop tuberculosis they appear to have a better chance of recovery than the others. It has not been ascertained in this study whether the immunity of the offspring is passive or acquired.

Cancer Mortality in the Ten Original Registration States.—SCHERESCHEWSKY (*U. S. Public Health Reports*, 1926, **4**, 1) has studied the death rate for cancer in the ten original registration states which comprise about one-fourth of the population of the continental United States. The various adjustments necessary are made and special mention is given to the possible improvement in the diagnosis of this disease. But it is pointed out that while internal cancer may be more frequently recognized than in earlier years this would not hold for cancer of the breast, mouth and female genitals. The possible influence of racial stock as influenced by immigration is discussed and discarded. The following are the conclusions: (1) There has been a pronounced increase in the observed death rate from cancer in persons forty years and over in that part of the United States known as the 10 original registration states; (2) part of this increase (about 30 per cent) is due to greater precision and accuracy in filling out death returns; (3) the remainder, however, is an actual increase in the mortality resulting in a death rate between 25 and 30 per cent higher than it was twenty-one years ago.

Some Studies on the Incidence of Goiter among School Children in Manitoba.—HAMILTON (*Can. Med. Assn. J.*, 1925, **15**, 1017) states that a goiter survey of 2329 children in the city of Winnipeg and several

country points in Manitoba showed that there is a high incidence of goiter among school children in Manitoba. There is no marked difference between the sexes in the earlier school ages. With increasing age goiter predominates in girls; after puberty there is an apparent general reversion toward normal among boys; this is not so marked among girls. The marked variation in the incidence of goitrous enlargement in different sections of the city may be accounted for by the fact that the citizens live in "racial districts" and that there is an apparent difference in the susceptibility of the various races. This shows itself both in the total goitrous incidence and in the degree of severity. The Scotch, English and Irish show much less goiter than the Ruthenians, Polish, Jewish and German. The findings indicate the possible importance of causative factors other than the water supply, food and cleanliness being the most probable ones.

Smallpox Vaccination as Carried Out at Lehigh University.—THOMAS (*U. S. Public Health Reports*, 1926, **41**, 37) notes the objection on the part of the general public to smallpox vaccination and points out some of the disastrous consequences of this. He believes that much of the objection could be overcome if certificates could be issued, not only in cases of typical takes, but also in those giving an "immune reaction." The technique of vaccination is described as follows: "Exactly the same technique was followed in each case. The skin of the upper arm was cleansed by rubbing with a swab of cotton saturated with alcohol. This was allowed to dry. With his left arm the operator grasped, from below, the arm of the patient, in the region of the insertion of the deltoid muscle. The skin was stretched and three short, parallel scratches were made about three-quarters of an inch apart. The scratches penetrated the epidermis but pains were taken not to draw blood. Care was taken not to include any scar tissue from previous vaccinations in the stretched area. The virus was expelled from the tube on the two outside scratches and rubbed in thoroughly. The middle scratch was not inoculated but served as a control. It received the same degree of trauma as the two inoculated scratches." Data are presented on the results of vaccination in a large number of vaccinations. The significance of scars is discussed and it is shown that not much dependence is to be placed on them as an index of immunity.

PHYSIOLOGY.

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA.

SESSION OF APRIL 19, 1926.

Conductivity Changes in Normal and Pathologic Insect Blood.—NELLIE M. PAYNE (from the Department of Zoölogy, University of Pennsylvania). Conductivity changes in insect blood were studied chiefly in the Japanese beetle, Popillia japponica Neum. Readings

were made by means of the "ionometer" and are reported here without protein correction. Conductivity studies were made in connection with the problem of the physicochemical changes associated with cold hardiness. The total range of conductivity thus far observed is from 0.06 to 0.80 expressed in per cent NaCl equivalent. The highest conductivities occur in dehydrated insects and the lowest in those infected with wilt disease. With the same external relative humidity, the lower the temperature the greater the conductivity. Cold hardiness can be measured by conductivity. With the lowest conductivity is the least cold hardiness. The changes occurring during the course of wilt disease were followed by means of conductivity measurements.

Electromotive Phenomena in Teeth and Bones.—W. R. AMBERSON, R. W. WILLIAMS, and H. KLEIN (from the Department of Physiology, University of Pennsylvania). Clinical studies of the electromotive phenomena of the mouth show that the dentine of the human and cats' teeth is almost always galvanometrically positive to the enamel of the same tooth (27 out of 29 teeth examined), the E.M.Fs ranging from 3.5 to 24.1 millivolts. This condition resembles the "injury current" of nerve and muscle and is believed to arise from similar causes, the enamel forming a semipermeable membrane with a differential permeability for anions and cations leading to the development of an electrical double layer across it. This conclusion is confirmed by laboratory studies on excised human and dogs' teeth. The pulp is removed and the pulp cavity enlarged. The tooth is then run through changes of M/10 KCl until the other salts originally present are removed, and the tooth structure is impregnated with the KCl. The tooth is then sealed to a glass tube in such a manner that the pulp cavity and the tube can be filled with M/10 KCl. The tip of the tooth is brought into contact with an outside solution of M/10 KCl. Electrical connection from the two solutions to the potentiometer is made through two calomel half cells, made up with M/10 KCl. Under these conditions the system shows little or no E.M.F. If now the external solution is replaced by M/50, M/250, and M/1250 KCl in succession, larger E.M.Fs are observed, increasing with each dilution. The external solution becomes more and more positive. Thus in a typical experiment the following values were obtained:

$\frac{M}{10}$ KCl inside against $\frac{M}{10}$ KCl outside 0.0027 v.

$\frac{M}{10}$ KCl inside against $\frac{M}{50}$ KCl outside 0.0284 v.

$\frac{M}{10}$ KCl inside against $\frac{M}{250}$ KCl outside 0.0632 v.

$\frac{M}{10}$ KCl inside against $\frac{M}{1250}$ KCl outside 0.0967 v.

Other monovalent salts give similar results. These values are similar in direction and magnitude to those observed by Loeb and Beutner[1] Michaelis and Fujita[2] and others across the apple skin and similar membranes. Similar effects can be demonstrated across bone and egg shell, the values, however, being considerably lower than across the enamel. When the enamel is removed from the tooth, and the dentine alone used, the electromotive effects largely disappear. These comparative studies indicate that the physical structure of the membrane (size of pores, etc.) is important in determining the magnitude of the effects and that they do not arise because of the presence of any particular chemical substance, such as lipoid, as Beutner[3] has suggested, or protein, as Hoeber[4] and Mond[5] have maintained. The results further indicate that the differential permeability for anions and cations is probably determined by the electrical charge upon the membrane. Under the conditions above described the enamel behaves as if negatively charged, this charge repelling anions and preventing their passage but permitting the passage of cations. The membrane charge can be diminished or reversed by previous treatment of the teeth with various concentrations of $CaCl_2$. With high $CaCl_2$ concentrations the enamel behaves as if positively charged, and the concentration effects is reversed in polarity, the more dilute external solution becoming more and more negative, as if anions could now pass but not cations. Barium and strontium salts have a similar influence. These membranes furnish a highly durable material for the study of membrane potentials, permit the demonstration of a whole series of effects upon one preparation, and seem to furnish an excellent opportunity for the study of the physical factors involved in permeability.

The Effect of the Administration of Cod Liver Oil on Thyroparahyroidectomized Dogs.—J. H. Jones (from the Department of Physiological Chemistry School of Medicine, University of Pennsylvania, Philadelphia). The removal of the parathyroid glands from dogs has been found to cause a rapid fall in the concentration of serum calcium followed by tetany and death. The tetany and death have often been ascribed to the low calcium in the serum. With control dogs which for two weeks previous had been fed a basal ration consisting of equal parts of autoclaved rolled oats and ground corn, *ad libitum*, supplemented with 5 gm. of casein and 2 gm. of sodium chlorid per day, similar results were obtained following thyroparathyroidectomy. In accordance with the findings of other investigators, the concentration of serum calcium dropped in the course of two to three days from a normal of 10 mg. per 100 cc. of serum to 6 or 7 mg. with the simultaneous onset of tetany which terminated in death soon afterward. In no case did the dogs live longer than five days. Cod liver oil and ultraviolet radiations were administered after the glands had been removed without beneficial effect. But, if prior to the operation, 20 cc. of cod liver oil per day were fed for two weeks the removal of the glands failed to produce tetany

[1] Biochem. Zeits., 1912, **41**, 1.
[2] Biochem. Zeits., 1925, **158**, 28.
[3] Die Entstehung Elektrischer Strome in Lebenden Geweben, Stuttgart, 1920.
[4] Zeits. f. physikal. Chem., 1924, **110**, 142.
[5] Pflug. Archiv. f. d. ges. Physiol., 1924, **203**, 247.

and the length of life of the animals was greatly increased. Three dogs so treated lived respectively twenty-one, forty-nine and fifty-four days. Two animals which received the oil for seven days before the operation died on the seventeenth and twenty-first days respectively. Single instances of slight tetany were observed in each of the last two experiments. The calcium in the blood of the treated animals fell as rapidly as that of the untreated animals, and, in fact, the lowest levels attained were in the blood of the treated dogs which lived the longest. In several cases the calcium content of the serum decreased to 4 or 5 mg. per 100 cc. The lowest concentration to which it dropped in the serum of these animals was 3.98 mg. whereas no determination of the calcium in the serum of the untreated animals was below 5.92 mg. These data indicate that some factor in addition to the low calcium plays a part in the production of the tetany and death, and it is probably on this factor that cod liver oil exerts its influence. Similar results, but not as striking, were obtained by irradiating the dogs with ultraviolet light before the removal of the glands.

The Photoelectric Cell as a Colorimeter.—S. P. REIMANN (from the Pathology Department, The Lankenau Hospital). The particular cell used was an argon filled tube. After suitable experimentation it was found possible to use the sensitivity of this cell to illumination as a measure of the amount of light held back by differing densities of color as produced by different concentrations of chemicals, for instance, dextrose developing a blue color as in the Folin-Wu method. The cell has been found to be sufficiently sensitive in all colors of the spectrum to be useful in other colors. Under certain limitations the cell is far more sensitive than the human eye and by the use of proper color screens, very accurate determinations can be made. Full details will be published shortly.

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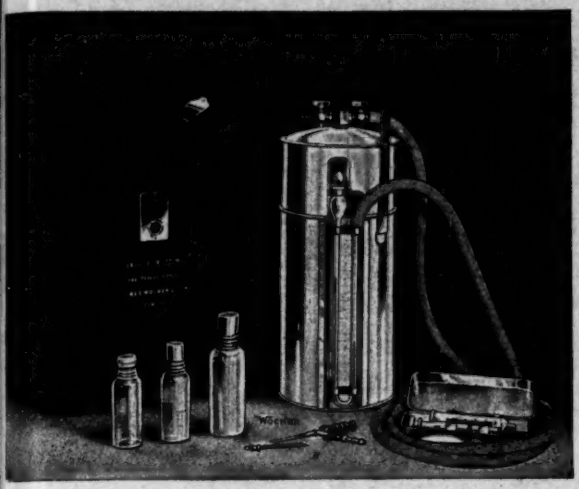

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